Clinical Experience with Linezolid for the Treatment of Nocardia Infection

Edina H. Moylett,1 Susan E. Pacheco,1 Barbara A. Brown-Elliott,2 Tracy R. Perry,1 E. Stephen Buescher,4
Mary C. Birmingham,5 Jerome J. Schentag,6 Joseph F. Gimbel,7 Aaron Apodaca,8 Margot A. Schwartz,9
Robert M. Rakita,3 and Richard J. Wallace, Jr.2

1Department of Pediatrics, Section of Allergy and Immunology, Texas Children’s Hospital, Houston, and 2Department of Microbiology, University of Texas Health Center, Tyler, Texas; 3Department of Pharmacy, Kindred Hospital, Indianapolis, Indiana; 4Center for Pediatric Research, Eastern Virginia Medical School, Norfolk; 5Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital and 6University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, New York; 7Arizona Research Center, Phoenix; and Sections of 8General Internal Medicine and 9Infectious Diseases, Virginia Mason Medical Center, Seattle, Washington

Clinical Infectious Diseases 2003; 36:313–8

Received 24 July 2002; accepted 26 October 2002; electronically published 13 January 2003.
Financial support: Pharmacia (Peapack, NJ), which provided the treatment drug.
Reprints or correspondence: Dr. Edina H. Moylett, Texas Children’s Hospital, Dept. of Allergy and Immunology, 6621 Fannin St., 3rd Fl. (MC: FC330.01), Houston, TX 77030 (emoylett@bcm.tmc.edu).

Linezolid is an oxazolidinone that has activity against most gram-positive bacteria, including in vitro activity against all Nocardia species and strains. We describe 6 clinical cases of nocardiosis that were successfully treated with linezolid. Two patients had underlying X-linked chronic granulomatous disease, and 2 patients were receiving chronic corticosteroid therapy. Four of 6 patients had disseminated disease, and 2 of these 4 patients had multiple brain abscesses. Four patients primarily received monotherapy; for the fifth patient, linezolid was added to a failing multiple-drug regimen, and, for the sixth patient, it was used as part of combination therapy. All 6 patients were successfully treated, although 1 patient had a presumed relapse of central nervous system infection after premature discontinuation of the drug. Linezolid appears to be an effective alternative for the treatment of nocardiosis.

Linezolid is a synthetic antibacterial agent of a novel class of antibiotics, the oxazolidinones, which has clinical usefulness in the treatment of infections caused by aerobic gram-positive bacteria. Linezolid binds to a site on the bacterial 23S rRNA of the 50S subunit and prevents the formation of a functional 70S-initiation complex, which is an essential component of the bacterial translation process [1]. This mechanism of action is different from that of other antimicrobial agents; therefore, cross-resistance with other classes of antimicrobials has not been encountered. Linezolid is primarily targeted at the treatment of infections secondary to resistant gram-positive organisms, especially methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus species. However, linezolid also has in vitro activity against some gram-negative anaerobes as well as some atypical organisms [1].

Nocardia species cause infection in humans and animals. Twelve species (or taxa) within the genus Nocardia have been identified using advanced laboratory techniques. Of these species, the best known is Nocardia asteroides sensu stricto. The latter term specifies that the current species grouping excludes Nocardia nova, Nocardia farcinica, and Nocardia transvaalensis, which, in older studies, were not recognized as species and were included in what was called “N. asteroides” or “N. asteroides complex.” N. farcinica, N. nova, Nocardia brasiliensis, Nocardia otitidiscaviarum, and N. transvalensis complex are other species frequently associated with infection in humans [2]. Members of the N. asteroides complex (older definition) are responsible for ~80% of noncutaneous invasive disease and for most systemic and CNS disease. N. farcinica is most often
Table 1. Clinical features of disease, indications for linezolid use, and outcomes for 6 patients with nocardiosis treated with linezolid.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in years, sex</th>
<th>Underlying medical condition or drug use</th>
<th>Type of clinical nocardiosis syndrome</th>
<th>Previous antibiotic therapy (duration)</th>
<th>Indication(s) for starting Lzd</th>
<th>Lzd dosage</th>
<th>Duration of Lzd therapy, months</th>
<th>Adverse events attributed to Lzd therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45, M</td>
<td>Silicosis and steroid use</td>
<td>Disseminated (skin pustules and multiple brain abscesses [figure 1])</td>
<td>TMP-SMX and Ctri (3 weeks)</td>
<td>Diffuse rash, fever, and elevated transaminase levels that resolved with discontinuation of TMP-SMX; long-term iv therapy is not an option</td>
<td>600 mg po b.i.d.</td>
<td>12</td>
<td>None</td>
<td>Clinical cure (figure 2)</td>
</tr>
<tr>
<td>2</td>
<td>63, M</td>
<td>Silicosis and steroid use</td>
<td>Disseminated (skin pustules and pulmonary nodules)</td>
<td>None</td>
<td>History of sulfonamide allergy (skin rash)</td>
<td>600 mg po b.i.d.</td>
<td>3</td>
<td>Anemia</td>
<td>Suspected recurrence of CNS infection*</td>
</tr>
<tr>
<td>3</td>
<td>54, F</td>
<td>None</td>
<td>Facial cellulitis and pustules</td>
<td>Dcl (3 weeks)</td>
<td>Clinical failure as part of phase-3 Lzd skin and skin structure infection protocol</td>
<td>600 mg po b.i.d.</td>
<td>2</td>
<td>Anemia</td>
<td>Clinical cure</td>
</tr>
<tr>
<td>4</td>
<td>52, F</td>
<td>None</td>
<td>Disseminated (brain, lung, mediastinal nodes, liver, kidney, and adrenal glands)</td>
<td>TMP-SMX (4 weeks); switched to Mino and Cpfx (1 week)</td>
<td>Diffuse rash, myelosuppression, and elevated transaminase levels that resolved with discontinuation of TMP-SMX; after the switch: severe clinical disease, intermediate in vitro susceptibility to Mino and Cpfx</td>
<td>600 mg po or iv b.i.d.</td>
<td>4</td>
<td>Anemia, thrombocytopenia, lactic acidosis, and peripheral neuropathy [16]</td>
<td>Clinical cure; patient completed 8 weeks of Lzd and Clm* as well as 7 weeks of Lzd and Gati; completed therapy with Moxi as a result of adverse events attributed to Lzd</td>
</tr>
<tr>
<td>5</td>
<td>6, M</td>
<td>CGD</td>
<td>Pulmonary (new-onset cavitary pneumonia [figure 3]; history of <em>N. brasiliensis</em> pneumonia necessitating right pneumonectomy)</td>
<td>TMP-SMX and Tic/Civ (10 days); Amik added on day 10; Lzd and Mero added on day 28</td>
<td>Rapidly worsening lung disease, daily spiking fever, doubling in size of initial pulmonary lesion while following the initial antibiotic regimen</td>
<td>10 mg/kg iv b.i.d.</td>
<td>1.5 or 24.5*</td>
<td>None</td>
<td>Clinical cure (figure 4); patient completed 8 weeks of Lzd and Gati; 7 weeks of Lzd and Tic/Civ, 6 weeks of Lzd iv, and 5 weeks of Mero; patient received 6 granulocyte transfusions</td>
</tr>
<tr>
<td>6</td>
<td>9, M</td>
<td>CGD</td>
<td>Disseminated (nasal abscess and bilateral nodular pneumonia)</td>
<td>TMP-SMX and Amik (7 days); TMP-SMX alone (3 days)</td>
<td>With TMP-SMX alone, extensive erythema and conjunctival injection 10 days after rapid oral desensitization</td>
<td>300 mg po b.i.d.</td>
<td>12</td>
<td>None</td>
<td>Clinical cure</td>
</tr>
</tbody>
</table>

**NOTE.** Amik, amikacin; CGD, chronic granulomatous disease; Clm, clarithromycin; Cpfx, ciprofloxacin; Ctri, ceftriaxone; Dcl, dicloxacillin; Gati, gatifloxacin; Lzd, linezolid; Mero, meropenem; Mino, minocycline; Moxi, moxifloxacin; *N. brasiliensis*, Nocardia brasiliensis; Tic/Civ, ticarcillin-clavulanate; TMP-SMX, trimethoprim-sulfamethoxazole.

* Within 3 weeks of discontinuing linezolid, the patient developed fever and an abnormal affect, which necessitated admission to the hospital. MRI of the brain revealed no abnormal findings, and fever and neurological findings resolved synchronously. Suspected relapse of *Nocardia* infection was treated with 6 weeks of therapy with ceftriaxone and TMP-SMX (after successful desensitization), and 12 months of therapy with TMP-SMX were completed.

* Lzd therapy was followed by long-term suppressive oral therapy with TMP-SMX.

* Clm was switched to Gati as a result of severe nausea and vomiting.

* For intravenous therapy.

* For oral therapy.
Figure 1. Gadolinium-enhanced MRI of the brain (patient 1). Multiple lesions throughout the cerebral hemispheres are revealed (arrows), indicating multiple abscesses.

Figure 2. Follow-up MRI of the brain of patient 1 after he completed 12 months of linezolid therapy. The previously demonstrated CNS lesions have resolved.

associated with antibiotic resistance [3], and >50% of cases involve disseminated infection [4]. The relative virulence of N. asteroides complex correlates with the ability to inhibit important phagocyte functions, thereby enabling the organism to exist indefinitely within the host [5].

Nocardia species are primarily opportunists, and infection occurs more frequently in patients with an underlying immunocompromised status. Procedures, conditions, and therapies associated with nocardiosis include organ transplantation, malignancy, diabetes mellitus, alcoholism, AIDS, and long-term use of corticosteroids [6]. Nocardia infection has been reported in patients with underlying chronic granulomatous disease [7].

Sulfonamides have comprised the cornerstone for the treatment of nocardiosis since the 1940s [8]. Combination therapy with a carbapenem or a third-generation cephalosporin with or without amikacin usually is recommended for severely ill patients or for those with CNS involvement [2], for whom the mortality rate approaches 50% when a sulfonamide alone is received. New antimicrobial agents are desirable, given the increasing number of reports of resistance to sulfonamides [9, 10], the relatively high incidence of adverse events occurring during sulfonamide therapy (most notably, among HIV-infected patients) [11], and the lack of alternative highly active oral agents.

In vitro studies of the antimicrobial activity of linezolid against clinical strains of Nocardia species have revealed that all strains are inhibited by a concentration of ≤8 \( \mu \)g/mL [12, 13]. However, data from in vivo studies are lacking. We describe the successful use of linezolid for the treatment of Nocardia infection in 6 patients (4 adults and 2 children). To our knowledge, this is the first report in the medical literature that describes the use of linezolid for patients with Nocardia infection.

PATIENTS AND METHODS

Patients with nocardiosis were identified through referral of clinical isolates to the University of Texas Health Center at Tyler for susceptibility testing. A diagnosis of Nocardia infection required a positive culture result for a sample obtained from a clinically affected site. Clinical isolates were tested at the Mycobacteria/Nocardia Research Laboratory at the University of Texas Health Center at Tyler. Species identification of each isolate was accomplished using PCR and restriction fragment–length polymorphism analysis of a 439-bp segment of the 65-kDa heat-shock protein gene, as described elsewhere [14]. Susceptibility testing was performed using serial 2-fold microdilution in cation-supplemented Mueller-Hinton broth, as previously described and recommended by the National Committee for Clinical Laboratory Standards [15].

Table 1 shows the demographic characteristics, clinical manifestations, previous antimicrobial therapy, indications for linezolid use, and outcomes for the 6 patients with confirmed nocardiosis who were treated with linezolid; figures 1 and 2 provide a comparison of the MRIs of patient 1, and figures 3 and 4 provide a comparison of the CT scans of patient 5. Table 2 shows the antibiograms for each clinical isolate.

DISCUSSION

To our knowledge, this is the first report that describes the use of linezolid for the treatment of Nocardia infection. Four of the 6 patients described had underlying predisposing factors, as is frequently observed with this pathogen [2, 6]. In addition, patient 5, who had underlying chronic granulomatous disease, experienced recurrent Nocardia pneumonia (due to N. brasiliensis, followed by N. asteroides sensu stricto), despite receiving
Figure 3. CT scan of the chest of patient 5 revealing a large left upper lobe pneumonia with evidence of central cavitation as well as a previous right pneumonectomy.

appropriate prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX). A clinical cure was obtained for all patients, although patient 2, for whom therapy was discontinued prematurely, had a probable recurrence of CNS infection. Linezolid was generally well tolerated by each patient (most notably, by patient 3, for whom therapy was continued for >2 years). However, patient 4 developed significant adverse effects, including lactic acidosis and peripheral neuropathy, which resolved when linezolid therapy was discontinued, as recently reported [16].

Anemia developed in 3 patients, necessitating discontinuation of linezolid therapy for 2 patients (patients 2 and 4). CNS disease, a complication for which increased associated mortality is recognized [17], was documented in patients 1 and 4, for whom a clinical cure was documented after linezolid monotherapy (patient 1) and before switching to an alternative therapy (patient 4). Little is known about the adverse effects of long-term linezolid therapy. The drug is currently approved for short treatment courses only. However, treatment of nocardiosis requires therapy for 6–12 months. Knowledge of the toxicity associated with long-term linezolid therapy, its frequency, and its severity may help determine what role this drug or other, as-yet-to-be-developed oxazolidinones will play in the treatment of Nocardia infection.

Despite the development of numerous new drugs and classes of drugs during the past 60 years, sulfonamides continue to be the recommended treatment option for most cases of nocardiosis [2, 8]. The drug of choice most typically is TMP-SMX [18]. However, the principal reason for initiating linezolid therapy in this case series was a history of, or development of, intolerance to TMP-SMX (4 of 6 patients [67%]). For patients with a history of drug intolerance, desensitization to TMP-SMX is a therapeutic option, but it has been our experience that desensitization with sulfonamides generally has been unsuccessful and that it often has been followed by severe reactions, as demonstrated by patient 6 in this series. In addition, adverse effects of long-term use of TMP-SMX, including fever, rash, myelosuppression, and renal toxicity, are well recognized and are commonly problematic, especially among HIV-infected patients [11, 19, 20]. Antimicrobial agents that are alternatives to TMP-SMX should be considered for patients with infections caused by N. farcinica or N. otitidiscaviarum, which demonstrate inconsistent susceptibility to sulfonamides [21].

Isolated reports describing the use of alternative or additive oral antimicrobials for the treatment of nocardiosis, such as amoxicillin-clavulanate, minocycline, and fluoroquinolones, have appeared in the medical literature [22–25]. However, a narrow therapeutic margin or the absence of activity against all Nocardia species has severely limited the use of these potential alternative oral agents. The agents active against most Nocardia species are intravenously administered drugs, such as amikacin and ceftriaxone; however, not all Nocardia species are susceptible (N. transvalensis isolates are amikacin resistant, and N. farcinica isolates are ceftriaxone resistant). In addition, concerns related to cost, mode of administration, and toxicity often limit the use of these agents. For severely ill patients or patients...
with CNS disease, ≥2 or more drugs, which may include sulfonylamides, are frequently prescribed, despite the lack of controlled clinical trials, because of the poor results seen with the use of a sulfonamide or TMP-SMX alone [26].

In this case series, the oral antibiotic options considered to be alternatives on the basis of the results of the available antibiograms included minocycline for 3 of 6 patients, amoxicillin-clavulanate for 2 of 6 patients, and clarithromycin for 2 of 6 patients. Minocycline and amoxicillin-clavulanate have a low therapeutic index that makes their use as a single agent, especially for the treatment of patients with CNS disease, highly problematic. Clarithromycin may have been an alternative agent for patient 6; however, success with macrolides for the treatment of patients with nocardiosis primarily has been reported in association with N. nova (MIC, ≤0.25 μg/mL). Patient 4 received clarithromycin for 6 weeks before the onset of severe nausea and vomiting, which necessitated discontinuation of such therapy.

Thus, the major limitation in the treatment of nocardiosis has been the absence of a second oral antimicrobial with activity against all Nocardia species. Linezolid possesses a broad spectrum of in vitro and in vivo activity against a range of gram-positive bacteria [1] and is available in both intravenous and oral preparations. Brown-Elliott et al. [12] tested the susceptibility of 140 clinical isolates of Nocardia (7 species) to linezolid, including 25 isolates of N. farcinica, 6 isolates of N. transvalensis complex, and 4 isolates of N. otitidiscaviarum. By broth microdilution, the MIC₉₀ and MIC₅₀ for all species other than N. farcinica were determined to be 2 μg/mL and 4 μg/mL, respectively. The MIC₉₀ and the MIC₅₀ for N. farcinica were both 4 μg/mL. Vera-Cabrer et al. [13] examined the activity of linezolid against 25 strains of N. brasiliensis and obtained similar results. Susceptibility breakpoints have been suggested for linezolid at an MIC of ≤8 μg/mL [12, 15]. To date, no Nocardia isolates with an MIC of >8 μg/mL have been reported; therefore, no resistance breakpoints have been proposed.

CNS nocardiosis is associated with significant morbidity and mortality. A number of recent reports have highlighted the excellent penetration of the CSF by linezolid after intravenous administration of the drug every 12 h [27, 28]. Villani et al. [27] reported the CSF levels of linezolid in patients with gram-positive CNS infection. In the latter study, the ratio of CSF and plasma linezolid trough concentrations always exceeded 1, and of more importance, the CSF linezolid trough concentration largely exceeded the MICs of the gram-positive isolates being studied. Similar data concerning Nocardia CNS infection are not currently available; however, patients 1 and 4 in the present series demonstrate the efficacy of linezolid for the treatment of CNS nocardiosis.

Given linezolid’s excellent in vitro susceptibility profile against a range of Nocardia species, its 100% oral bioavailability, and its successful treatment of the 6 patients described in the present study, it would appear to be a valid alternative for the treatment of Nocardia infections in cases in which TMP-SMX has failed, where its use is contraindicated, or where a second agent is indicated. The drug may also be especially useful as

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Table 2. Antibiograms and species identification of the case isolates of Nocardia species recovered from 6 patients with confirmed nocardiosis.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>N. asteroidesᵃ from patient 1</th>
<th>N. asteroidesᵇ from patient 2</th>
<th>N. brasiliensis from patient 3</th>
<th>N. otitidiscaviarum from patient 4</th>
<th>N. asteroidesᵃ from patient 5</th>
<th>N. otitidiscaviarum from patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≤0.5 (S)</td>
<td>1 (S)</td>
<td>2 (S)</td>
<td>8 (S)</td>
<td>1 (S)</td>
<td>8 (S)</td>
</tr>
<tr>
<td>Amox/Clv</td>
<td>≤1/2 (S)</td>
<td>&gt;128/2 (R)</td>
<td>≤2/2 (S)</td>
<td>&gt;128/2 (R)</td>
<td>&gt;128/2 (R)</td>
<td>&gt;128/2 (R)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>4 (S)</td>
<td>32 (R)</td>
<td>&gt;64 (R)</td>
<td>Not done</td>
<td>16 (I)</td>
<td>&gt;32 (R)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>4 (S)</td>
<td>32 (I)</td>
<td>32 (I)</td>
<td>&gt;32 (R)</td>
<td>32 (I)</td>
<td>&gt;32 (R)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 (S)</td>
<td>32 (I)</td>
<td>32 (I)</td>
<td>&gt;32 (R)</td>
<td>32 (I)</td>
<td>&gt;32 (R)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>8 (R)</td>
<td>&gt;8 (R)</td>
<td>8 (R)</td>
<td>2 (I)</td>
<td>&gt;8 (R)</td>
<td>2 (I)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&gt;16 (R)</td>
<td>&gt;16 (R)</td>
<td>&gt;16 (R)</td>
<td>≤0.25 (S)</td>
<td>&gt;16 (R)</td>
<td>2 (S)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>16 (R)</td>
<td>8 (I)</td>
<td>&gt;32 (R)</td>
<td>&gt;32 (R)</td>
<td>8 (I)</td>
<td>&gt;32 (R)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1 (S)</td>
<td>2 (S)</td>
<td>4 (S)</td>
<td>2 (S)</td>
<td>2 (S)</td>
<td>4 (S)</td>
</tr>
<tr>
<td>Minocycline</td>
<td>≤1 (S)</td>
<td>2 (S)</td>
<td>8 (R)</td>
<td>2 (I)</td>
<td>4 (I)</td>
<td>4 (I)</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>2 (S)</td>
<td>4 (S)</td>
<td>16 (S)</td>
<td>8 (S)</td>
<td>4 (S)</td>
<td>16 (S)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1 (S)</td>
<td>≤0.25 (S)</td>
<td>1 (S)</td>
<td>4 (S)</td>
<td>≤0.25 (S)</td>
<td>4 (S)</td>
</tr>
</tbody>
</table>

NOTE.  Amox/Clv, amoxicillin/clavulanate; I, intermediately susceptible; R, resistant; S, susceptible.

ᵃ In micrograms per milliliter.
ᵇ Nocardia asteroides sensu stricto.
ᶜ Susceptibility to moxifloxacin and gatifloxacin was determined by MICs of 0.5 μg/mL.
initial therapy until susceptibility results for other potential agents are available. In addition, the cytochrome P-450 enzymatic complex neither participates in linezolid metabolism nor undergoes induction or inhibition by linezolid or its metabolites, making drug interactions less of a concern. The latter is particularly beneficial with regard to the treatment of patients already following complex medical regimens, such as patients with HIV/AIDS or organ transplant recipients. However, a potential disadvantage to prescribing long-term suppressive oral linezolid therapy is the cost (~$35,000 for 12 months of treatment, on the basis of twice-daily administration). In addition, the adverse effects of long-term therapy have not been fully delineated at this time. Therefore, although linezolid is a welcome and useful addition to the armamentarium for the treatment of nocardiosis, at this time, it is an excellent potential second-line agent.

Acknowledgment

We thank Pharmacia (Peapack, NJ), which provided the drug used in the treatment of the patients in this study.

References