Linezolid in the Treatment of Multidrug-Resistant Tuberculosis

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Background. Linezolid is a new antibiotic with activity against *Mycobacterium tuberculosis* in vitro and in animal studies. Several small case series suggest that linezolid is poorly tolerated because of the side effects of anemia/thrombocytopenia and peripheral neuropathy. To characterize our clinical experience with linezolid, the California Department of Public Health Tuberculosis Control Branch's Multidrug-Resistant Tuberculosis (MDR-TB) Service reviewed cases in which the MDR-TB treatment regimens included linezolid therapy.

Methods. Record review was performed for 30 patients treated with linezolid as part of an MDR-TB regimen. Data were collected on clinical and microbiological characteristics, linezolid tolerability, and treatment outcomes. The dosage of linezolid was 600 mg daily. Vitamin B6 at a dosage of 50–100 mg daily was used to mitigate hematologic toxicity.

Results. During 2003–2007, 30 patients received linezolid for the treatment of MDR-TB. Patients had isolates resistant to a median of 5 drugs (range, 2–13 drugs). Of the 30 cases, 29 (97%) were pulmonary; of these 29, 21 (72%) had positive results of acid-fast bacilli smear, and 16 (55%) were cavitary. Culture conversion occurred in all pulmonary cases at a median of 7 weeks. At data censure (31 December 2008), 22 (73%) of 30 patients had successfully completed treatment. Five continued to receive treatment. There were no deaths. Three patients had a poor outcome, including 2 defaults and 1 treatment failure. Side effects occurred in 9 patients, including peripheral and optic neuropathy, anemia/thrombocytopenia, rash, and diarrhea. However, only 3 patients stopped linezolid treatment because of side effects.

Conclusions. Linezolid was well tolerated, had low rates of discontinuation, and may have efficacy in the treatment of MDR-TB.

Linezolid, the first oxazolidinone approved for clinical use, has shown good activity against drug-resistant strains of *Mycobacterium tuberculosis,* both in vitro and in animal studies [1–3]. Linezolid is rapidly and extensively absorbed after oral dosing [4]. It readily distributes to well-perfused regions of the body, penetrates well into bronchoalveolar tissues, and acts by inhibiting protein synthesis at an early stage of translation [5]. Recent case series have reported clinical and radiographic improvement among patients with multidrug-resistant tuberculosis (MDR-TB) whose treatment regimens included linezolid and for whom no acceptable alternative existed among other available drugs [6, 7]. Moreover, the rapid lowering of the bacillary load observed with the addition of linezolid among patients with MDR-TB with fluoroquinolone and/or aminoglycoside resistance [8] and patients receiving failing regimens suggests promising efficacy [9]. Linezolid's safety and tolerability are limited by the dose- and duration-dependent occurrence of reversible myelosuppression and peripheral and optic neuropathy [10–12]. Despite these toxicities, cures have been reported among patients with MDR-TB treated with a linezolid-containing regimen [7, 13]. Published clinical experience with linezolid and MDR-TB has generally been limited by small sample sizes. A larger series may provide additional information on linezolid's role in treating drug-resistant tuberculosis. We report on the California experience with linezolid in 30 patients with MDR-TB during a period of 5 years.

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California reports 30–40 patients with MDR-TB and 0–4 patients with extensively drug-resistant tuberculosis (XDR-TB) annually. The California Department of Public Health Tuberculosis Control Branch's MDR-TB Service provides clinical consultation and technical expertise to local health jurisdictions to manage these challenging tuberculosis cases. To further characterize linezolid's safety, tolerability, and long-term treatment outcomes, the MDR-TB Service conducted a retrospective record review of patients whose regimens included linezolid.

MATERIALS AND METHODS

All MDR-TB cases in California with MDR-TB Service consultation that were treated with linezolid as part of an MDR-TB regimen from 1 January 2003 through 31 December 2007 were reviewed. Data review was censured on 31 December 2008.

All patients received linezolid as part of an expanded tuberculosis treatment regimen, tailored to the susceptibility results of each isolate and given by directly observed therapy throughout treatment. Treatment duration varied but was a minimum of 18 months. Treatment regimens included linezolid and $\geqslant$3 second-line companion drugs selected according to individual drug history and recent susceptibility results. Linezolid was administered orally at a dosage of 600 mg daily to all but 2 patients. One patient received 450 mg of linezolid daily, and the other received 600 mg 3 times a week, adjusted for body weight <40 kg. Treatment regimens also included vitamin B6 at a dosage of 50–100 mg daily, to reduce the risk of hematologic toxicity.

We abstracted state tuberculosis registry records and individual case data maintained as part of the MDR-TB Service, after personal identifiers were removed. Data included patient demographic characteristics and comorbid conditions; clinical, radiographic, and microbiological characteristics; serial sputum testing and culture results; treatment regimens, durations, and outcomes; and regimen toxicity and tolerability. We examined the treatment outcome of linezolid-containing regimens by clinical and radiographic improvement and by sputum smear and culture conversion. We examined safety and tolerability of linezolid by reviewing monthly complete blood count data and monthly inquiries regarding neuropathy. Myelosuppression, peripheral neuropathy, and optic neuropathy were assessed as linezolid related for this analysis. We assessed anemia and thrombocytopenia as mild (hemoglobin level, 10.0–13.0 g/dL; platelet count, $100–150 \times 10^9$ platelets/L), moderate (8.0–9.9 g/dL; $50–99 \times 10^9$ platelets/L), or severe (<8.0 g/dL and $< 50 \times 10^9$ platelets/L) [14], according to observed hemoglobin and platelet levels. Because this study used routinely collected surveillance and treatment data without patient identifiers, institutional review board approval was not required. Data were analyzed using Excel, 2003 (Microsoft).

Standard definitions were used for MDR-TB (ie, tuberculosis with documented resistance to at least isoniazid and rifampin) and XDR-TB (ie, MDR-TB with additional resistance to any fluoroquinolone antibiotic and at least 1 of 3 injectable drugs: capreomycin, amikacin, or kanamycin) [15]. For pulmonary cases, cure was defined by at least 2 consecutive negative cultures and no positive culture during the last 18 months of treatment, including an end-of-treatment specimen. For extrapulmonary cases, cure was defined by treatment completion with no clinical or radiological signs of activity. An unsatisfactory outcome was defined as default, treatment failure, relapse, or death.

RESULTS

Demographic characteristics. From 1 January 2003 through 31 December 2007, there were 174 cases of MDR-TB reported to the California tuberculosis case registry, of which 73 had consultation provided by the MDR-TB Service. A total of 30 patients to whom consultation was provided were treated with linezolid as part of a multidrug regimen for MDR-TB. The large majority of patients treated with linezolid were foreign born (87%), similar to all California tuberculosis case patients (77%) and California MDR-TB case patients (85%). The countries of origin included Laos (5 patients), India (4), Mexico (4), Thailand (3), Philippines (2), China (2), Vietnam (2), Cambodia (1), Marshall Islands (1), Mongolia (1), and Nepal (1). Four patients were US born. Sex distribution was equal. At the time of MDR-TB treatment initiation, the mean patient age was 38 years (range, 17–79 years).

Human immunodeficiency virus (HIV) status was documented to be negative for 17 (57%) of the 30 patients. No patients were known to the local health jurisdiction to have HIV or AIDS.

Disease status. Of the 30 patients, 14 (47%) had a history of previous treatment for tuberculosis. Twenty-nine (97%) of the 30 patients had pulmonary disease. One patient had Pott disease. Of the 29 patients with pulmonary tuberculosis, 16 (55%) had cavitary changes noted on initial chest radiograph or chest computed tomography, and 21 (72%) had positive sputum-smear microscopy results at the time of MDR-TB diagnosis. Twenty-nine patients had positive cultures; the drug-susceptibility test results are shown in Table 1. One patient had a positive result of sputum smear and had a molecular beacon test for isoniazid and rifampin resistance [16] performed on her clinical specimen, which showed the presence of katG and rpoB mutations, but her specimen was unable to be cultured. The median number of drugs to which the 29 culture-positive isolates were resistant was 5 (range, 2–13 drugs). Three (10%) of the 30 cases were XDR-TB.

Treatment. The median number of drugs used for MDR-TB treatment was 5, and each regimen included a fluoroquinolone and an injectable agent unless resistance was noted to

Table 1. Demographic Characteristics of Patients with Multidrug-Resistant Tuberculosis (MDR-TB) and Treatment Data

Case patient	Sex; age (in years) at treatment initiation	Cavitary status at time of MDR-TB diagnosis	Sputum smear result at time of MDR-TB diagnosis	Resistance pattern (in addition to INH and RIF resistance)	Drug regimen	Duration of MDR-TB treatment,[a] months
1	M; 64	Noncavitary	Negative	ETA	PZA, EMB, LZD, AMK, LFX	22
2	M; 20	Cavitary	Positive	EMB, PZA, STM, ETA, LFX, CPX, OFX, RIB	LZD, AMK, PAS, CYS, CFZ	18
3	F; 19	Cavitary	Negative	EMB, PZA, STM, KM, AMK, CPM, PAS, LFX, CPX, OFX, RIB	LZD, CPM, PAS, CYS, AZM	25
4	M; 38	Cavitary	Positive	EMB, PZA, STM	LZD, CPM, PAS, MFX, CYS	26
5	M; 17	Cavitary	Positive	EMB, STM, KM, AMK, ETA	PZA, LZD, CPM, PAS, LFX, CYS, RIB	26
6	M; 17	Noncavitary	Positive	EMB, STM, KM, AMK	PZA, LZD, CPM, ETA, MFX, CYS	36
7	F; 18	Noncavitary	Positive	EMB, STM, KM, AMK, ETA	PZA, EMB, LZD, CPM, PAS, LFX, CYS	27
8	M; 55	Cavitary	Positive	EMB, PZA, STM	LZD, AMK, PAS, ETA, MFX	29
9	M; 20	Noncavitary	Positive	EMB, PZA, STM	LZD, CPM, PAS, MFX, CYS	22
10	M; 17	Cavitary	Positive	EMB, STM, RIB	PZA, EMB, LZD, CPM, LFX	24
11	F; 79	Cavitary	Positive	EMB, STM	PZA, LZD, CPM, MFX, CYS	27
12	M; 47	Cavitary	Positive	EMB, PZA, STM	LZD, AMK, PAS, ETA, LFX	26
13	M; 66	Noncavitary	Negative	EMB, PZA, STM, PAS, RIB	LZD, CPM, ETA, MFX	8
14	F; 32	Noncavitary	Positive	EMB, PZA, STM, RIB	LZD, AMK, ETA, MFX	26
15	F; 20	Noncavitary	Negative	EMB, STM	PZA, LNX, ETA, MFX	22
16	F; 41	Noncavitary	Positive	EMB, PZA, STM, AMK	LZD, CPM, PAS, MFX, CYS	26
17	F; 21	Cavitary	Positive	EMB, PZA, STM, LFX, MFX, CPX, OFX, RIB	LZD, AMK, PAS, MFX, CYS	26
18	F; 23	Noncavitary	Positive	EMB, PZA, STM, ETA, RIB	LZD, AMK, PAS, MFX, CYS	22
19	M; 55	Cavitary	Positive	EMB, STM, KM, LFX	PZA, LZD, AMK, ETA, MFX, CYS	35
20	M; 39	Noncavitary	Positive	EMB, PZA, STM, LFX	LZD, CPM, PAS, ETA, CYS	26
21	M; 41	Cavitary	Positive	EMB, PZA, STM	LZD, CPM, PAS, MFX, CYS	10
22	F; 45	Cavitary	Negative	None[b]	PZA, EMB, LZD, CPM, ETA, MFX	18
23	F; 53	Cavitary	Positive	EMB, PZA, STM	LZD, CPM, ETA, LFX	20
24	F; 57	Noncavitary	Negative	No additional resistance	PZA, EMB, LZD, AMK, ETA, MFX, CYS	17
25	F; 21	Cavitary	Positive	PZA, MFX	EMB, LZD, CPM, PAS, LFX, CYS	25
26	M; 56	Noncavitary	Positive	EMB, PZA, STM, KM, CPX, OFX	LZD, CPM, PAS, LFX, CYS	Current
27	F; 58	Noncavitary	Negative	EMB, PZA, STM, CPX, RIB	LZD, CPM, PAS, ETA, LFX	Current
28	F; 30	Extrapulmonary	Extrapulmonary	EMB, PZA, ETA, LFX	LZD, AMK, PAS, MFX, CYS	Current
29	M; 45	Cavitary	Negative	EMB, STM, ETA, RIB	LZD, CPM, ETA, MFX, CYS	Current
30	F; 30	Cavitary	Positive	EMB, STM	PZA, LZD, AMK, ETA, MFX	Current

NOTE. AMK, amikacin; AZM, azithromycin; CFZ, clofazimine; CPM, capreomycin; CPX, ciprofloxacin; CYS, cycloserine; EMB, ethambutol; ETA, ethionomide; INH, isoniazid; KM, kanamycin; LFX, levofloxacin; LZD, linezolid; MFX, moxifloxacin; OFX, ofloxacin; PAS, para-aminosalicylic acid; PZA, pyrazinamide; RIB, rifabutin; RIF, rifampin; STM, streptomycin.

[a] "Current" indicates that the patient was still receiving treatment at data censure.

[b] Resistance to INH and RIF was determined by molecular beacon sequence analysis.

Table 2. Toxicities and Treatment Outcomes of Cases of Multidrug-Resistant Tuberculosis (MDR-TB)

Case	Time from start of MDR-TB treatment to culture conversion, weeks	Duration of linezolid therapy, months	Reported toxicity	Reason for discontinuing linezolid[a]	Treatment outcome
1	50	4	Anemia/thrombocytopenia	COT	Cure
2	13	18	None	COT	Cure
3	0	24	None	COT	Cure
4	4	23	None	COT	Cure
5	14	10	Vision loss/optic neuropathy	Vision loss	Cure
6	7	36	None	COT	Cure
7	11	25	None	COT	Cure
8	6	28	None	COT	Cure
9	10	22	None	COT	Cure
10	3	10	None	COT	Cure
11	9	26	None	COT	Cure
12	8	24	None	COT	Cure
13	0	6	None	Refused further treatment	Default, refused further treatment
14	10	25	Peripheral neuropathy	COT	Cure
15	0	22	None	Treatment stopped because failed	Failure
16	0	23	Rash, peripheral neuropathy	Linezolid interrupted and resumed; COT	Cure
17	4	25	None	COT	Cure
18	13	21	None	COT	Cure
19	42	25	None	COT	Cure
20	9	26	None	COT	Cure
21	4	1	Severe diarrhea, nausea	Severe diarrhea, nausea	Default, lost
22	0	18	None	COT	Cure
23	8	20	None	COT	Cure
24	0	5	Peripheral neuropathy	Intractable peripheral neuropathy (patient has diabetes)	Cure
25	4	25	None	COT	Cure
26	32	13	Peripheral neuropathy	Treatment current	Continued treatment
27	2	18	Peripheral neuropathy	Increased vitamin B6 dose, continued treatment; treatment current	Continued treatment
28	…[b]	17	Anemia	Treated with erythropoietin, continued treatment; treatment current	Continued treatment
29	1	14	None	Treatment current	Continued treatment
30	11	12	None	Treatment current	Continued treatment

NOTE. COT, completion of therapy.

[a] "Treatment current" indicates that the patient was still receiving linezolid treatment at data censure.

[b] Extrapulmonary case.

these classes of drugs. Indications for using linezolid were failure of previous MDR-TB treatment regimen or presence of extensive drug resistance or inability to tolerate other second-line drugs. The mean duration of linezolid administration was 18.9 months (range, 1–28 months). Table 1 shows the specific drugs used in each case.

One patient underwent a pneumonectomy in addition to his drug regimen. A second patient had extensive chest wall surgery for empyema necessitans.

Treatment outcomes. At data censure, 22 (73%) of the 30 patients had successfully completed therapy, with documented negative cultures for at least 18 months before the end of treatment, with 1 exception. That patient had 10 months of negative cultures before the end of treatment and has had follow-up for 3.5 years without relapse. Five patients (17%) are still receiving treatment. There were no deaths. Table 2 shows toxicities and treatment outcomes.

Only 3 (10%) of the patients had an unsatisfactory outcome.

Two patients defaulted. Of these, 1 refused to continue treatment after 27 weeks of therapy, because of intractable side effects. This patient had received previous treatment for tuberculosis in another country and had extensive fibrosis seen on chest radiograph, but only 1 sputum specimen of many obtained was positive for tuberculosis. He continues to be monitored at 6-month intervals without evidence of disease progression on radiograph and with negative sputum cultures. A second patient was lost to follow-up after 9.5 months of treatment. One patient had a treatment failure. This patient developed central line sepsis after ~10 days of intravenous capreomycin treatment. She refused further injectable therapy and was then placed on a 5-drug, all-oral regimen that included linezolid and moxifloxacin. The culture converted to negative quickly, but subsequently, her radiograph findings worsened, and cultures reverted to positive after 22 months of treatment.

For the 29 patients with pulmonary disease, all achieved conversion of culture to negative. The median time to culture conversion was 7 weeks after the initiation of MDR-TB therapy (range, 0–50 weeks).

Of the 22 patients who completed therapy, none have relapsed, after a mean follow-up of 1.5 years (range, 0–3.5 years). The remaining 5 patients receiving treatment were doing well at the time of data censure.

Treatment toxicity. Of the 30 patients, 21 (70%) had no reported significant toxicity likely attributable to linezolid therapy. Three patients stopped linezolid therapy because of side effects.

At baseline, 7 patients had mild-to-moderate anemia documented. Despite all patients receiving vitamin B6 as part of their regimen, 2 patients developed symptomatic anemia (hemoglobin levels, 10.6 and 8.6 g/dL) with dyspnea on exertion and fatigue while receiving linezolid, one of whom had moderate anemia at baseline. In 1 case, use of erythropoietin allowed the patient to continue to receive linezolid. This patient had not been anemic at treatment initiation. One patient developed mild thrombocytopenia (platelet count, 150×10^9 platelets/L). Despite these toxicities, no patients stopped linezolid treatment because of myelosuppression.

Peripheral neuropathy developed in 5 patients; for 1 of these patients, therapy with linezolid had to be discontinued after 5 months. This patient had poorly controlled diabetes. The remaining 4 patients were able to continue linezolid with careful monitoring of symptoms, with the plan to discontinue the drug if neuropathy progressed beyond the forefoot. In one instance, increasing the vitamin B6 dose from 150 mg to 200 mg appeared to resolve the neurologic complaints. Peripheral neuropathy did not resolve in the other 3 patients.

One patient developed visual loss secondary to optic neuropathy after 10 months of linezolid therapy. This patient also received rifabutin for 3 months. The patient developed worsening blurry vision and white spots in both visual fields. A neuro-ophthalmologic examination revealed findings consistent with linezolid-associated optic neuropathy. Following the immediate discontinuation of linezolid, visual acuity returned to normal over the course of 3–4 weeks. Linezolid was not restarted in this patient.

One additional patient developed severe, intractable diarrhea and nausea shortly after beginning linezolid, and the drug had to be discontinued because of these side effects, which resolved after discontinuation of linezolid. Lactic acidosis and serotonin syndrome, known toxicities of linezolid [17, 18], were not seen in our study. Rash was noted in one patient, but after rechallenge with all drugs in the regimen, including linezolid, the patient was able to complete therapy.

DISCUSSION

Compared with patients with pansusceptible tuberculosis, patients with MDR-TB and XDR-TB have significantly worse short- and long-term outcomes because of the lack of potent bactericidal drugs, the lengthy treatment duration of 18–30 months, and the difficult-to-tolerate side effects and toxicities of second-line medications used for treatment. Mitnick et al [19] presented the most optimistic treatment outcome results, suggesting that patients with XDR-TB treated in a community-based setting in Peru had a 60% cure rate.

Linezolid has been shown to be effective in the treatment of MDR-TB and XDR-TB in 5 case series [6–8, 13, 20]. However, several studies have found side effects and toxicities, primarily bone marrow suppression and peripheral and optic neuropathy, to be limiting factors in the use of linezolid. Park et al [6] report successful culture conversion in 8 HIV-negative patients but describe a high incidence of side effects even with a daily linezolid dose of 600 mg; 4 patients developed peripheral neuropathy, 2 developed optic neuropathy, and 1 developed anemia. Three patients discontinued treatment with linezolid, and 2 died of respiratory failure. The authors concluded that linezolid may be effective but is poorly tolerated. von der Lippe et al [7] reported a cohort of 10 patients with MDR-TB, 7 of whom developed significant side effects necessitating discontinuation of linezolid. Fortun et al [13] described successful treatment with linezolid for 5 patients with MDR-TB, but 4 patients developed severe anemia requiring blood transfusion at a dosage of 600 mg orally twice daily. In contrast, Condos et al [8] presented their findings for 7 patients with XDR-TB, showing initial culture conversion in all patients and a low incidence of hematologic and myelosuppressive side effects despite administration of the US Food and Drug Administration (FDA)–approved dosage of 600 mg orally twice a day (2 patients had peripheral neuropathy, and none had serious myelosuppressive side effects). Although 2 of 7 patients died, the authors concluded that linezolid is effective, safe, and tolerable and

postulated that the difference in tolerability in their case series may be attributable to close follow-up in a hospital or specialized tuberculosis unit setting. Migliori et al [20] reported 85 patients with MDR-TB and XDR-TB in Germany who were treated with linezolid. Thirty-two percent required discontinuation of treatment because of side effects. Discontinuation was significantly more frequent among patients receiving the 600-mg twice-daily dose.

The linezolid minimum inhibitory concentration (MIC) reported by the pharmaceutical company (Pfizer) for *M. tuberculosis* is 1 μg/mL. A cumulative weekly target area under the curve (AUC) of 350–700 μg$\times$h/mL is desired, which is based on the AUC/MIC ratio for gram-positive bacteria. For 7 daily doses of linezolid per week, the cumulative doses achieved an AUC/MIC ratio of 999 per week, which was above the desired target. On the basis of these data, we postulated that linezolid at a dosage of 600 mg once daily should be effective, with less toxicity.

Our case series is the largest from the United States on the use of linezolid-containing regimens for treatment of MDR-TB. We have reported on 30 patients receiving linezolid therapy at a dosage of 600 mg once daily (2 received intermittent or lower-dose therapy because of low body weight). Of the 30 patients, 22 successfully completed treatment. Among patients who completed treatment, there was no relapse during a mean follow-up of 1.5 years. All 29 patients with pulmonary tuberculosis achieved culture conversion, at a median time of 7 weeks. Five additional patients continued to receive treatment and were tolerating linezolid well at data censure. Two patients defaulted, and one experienced treatment failure, with an isolate with the same susceptibility pattern as the initial episode of MDR-TB. Linezolid discontinuation was necessary for only 3 patients: 1 because of progressive peripheral neuropathy, 1 because of onset of visual impairment from optic neuropathy that resolved after discontinuation of linezolid, and 1 because of intractable diarrhea that resolved after discontinuation of linezolid. Interestingly, 4 of 5 patients with peripheral neuropathy were able to continue linezolid, and myelosuppression, noted in only 2 patients, did not result in discontinuation of the medication. One patient with anemia was treated with erythropoietin, and one patient with thrombocytopenia was monitored closely. Both completed therapy with linezolid.

The low proportion of rate-limiting side effects and toxicities in our case series, in contrast to that in other reports, is likely multifactorial. First, we used a total daily dose of linezolid (600 mg) lower than the FDA-approved dose (1200 mg in 2 divided doses) for gram-positive organisms, which was used in most other MDR-TB case series. Second, the addition of vitamin B6 may have mitigated the bone marrow toxicity observed in other case series [21, 22]. Third, the use of colony-stimulating factors may be an effective adjunctive therapy in cases of anemia and may allow for continued treatment with linezolid if cost is not prohibitive. Fourth, HIV infection may predispose to peripheral neuropathy and myelosuppression, and none of our patients were known to be infected with HIV. Lastly, closely monitoring toxicities with ongoing expert consultation, rather than immediately discontinuing linezolid, may be helpful because most patients in our series did not have worse or escalating toxicities on continued therapy. This is an especially important point to emphasize as there are so few efficacious medications for the treatment of MDR-TB and XDR-TB. Managing side effects, while continuing the treatment regimen, is a very important principle in the treatment of these extremely difficult cases. Also, the linezolid side effect profile, although serious, has the advantage of infrequently causing gastrointestinal complaints and can often be added successfully when other second-line drugs used in MDR-TB treatment cannot be tolerated because of gastrointestinal problems.

There are several limitations to our study. First, although HIV status was not documented in every case, there were no known HIV-infected patients. It will be important to study linezolid tolerability and efficacy in an HIV-infected population. Second, since 53% of patients in our series did not report previous treatment for tuberculosis, this may have contributed to the good outcomes we found. Third, the decision to initiate linezolid treatment was sometimes made by a local health jurisdiction before consultation; therefore, there were not uniform criteria for use of the drug.

The optimal dose of linezolid that maximizes efficacy while minimizing toxicity remains to be defined. Our findings suggest that linezolid at a dosage of 600 mg once daily is well tolerated and appears to be an effective adjunctive medication in a treatment regimen tailored to susceptibility results for patients with complicated MDR-TB and XDR-TB with few other alternative treatment strategies.

Linezolid should be considered for use as an adjunct to the MDR-TB treatment regimen for patients with any of the following: XDR-TB; MDR-TB isolates resistant to all first-line drugs, a fluoroquinolone, or an injectable agent; extensive disease observed on chest radiograph or a high bacillary load as evidenced by bacteriologic studies; rapidly progressive and/or disseminated MDR-TB; or rapid amplification of drug resistance over time. The duration of treatment with linezolid is dependent on multiple factors, such as patient response, tolerability, and cost. We recommend the use of linezolid for the full duration of treatment if tolerated.

While receiving linezolid, patients should be closely monitored for signs or symptoms of bone marrow toxicity and peripheral and optic neuropathy. Bone marrow toxicity can be monitored with a complete blood count measured before starting and monthly throughout treatment, and neuropathy can be monitored by a monthly examination. Both should be com-

plemented by patient education about side effects. Patients should also be cautioned to report any adverse side effects while receiving linezolid, especially visual changes or sudden loss of vision. Vitamin B6 should be coadministered with linezolid.

CONCLUSION

We have found linezolid to be an effective addition to the armamentarium of drugs available to treat MDR-TB and XDR-TB. Efficacy was excellent as part of an optimized MDR-TB or XDR-TB regimen, with very acceptable toxicity. A randomized study of outcomes with linezolid treatment should be done.

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