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Linezolid use for treatment of multidrug-resistant and extensively drug-resistant tuberculosis, New York City, 2000–06

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Rationale: Linezolid may be effective for the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB); however, serious adverse events are common and there is little information on the management of these toxicities.

Methods: We retrospectively reviewed public health and medical records of 16 MDR TB patients, including 10 patients with XDR TB, who were treated with linezolid in New York City between January 2000 and December 2006, to determine treatment outcomes and describe the incidence, management and predictors of adverse events.

Results: Linezolid was added to MDR TB regimens for a median duration of 16 months (range: 1–29). Eleven patients (69%) completed treatment, four (25%) died and one (6%) discontinued treatment without relapse. Myelosuppression occurred in 13 (81%) patients a median of 5 weeks (range: 1–11) after starting linezolid, gastrointestinal adverse events occurred in 13 (81%) patients after a median of 8 weeks (range: 1–57) and neurotoxicity occurred in seven (44%) patients after a median of 16 weeks (range: 10–111). Adverse events were managed by combinations of temporary suspension of linezolid, linezolid dose reduction and symptom management. Five (31%) patients required eventual discontinuation of linezolid. Myelosuppression was more responsive to clinical management strategies than was neurotoxicity. Leucopenia and neuropathy occurred more often in males and older age was associated with thrombocytopenia ($P < 0.05$).

Conclusions: The majority of MDR TB patients on linezolid had favourable treatment outcomes, although treatment was complicated by adverse events that required extensive clinical management.

Keywords: MDR TB, XDR TB, oxazolidinones, toxicity, outcomes

Introduction

Tuberculosis (TB) control is challenged by multidrug-resistant (MDR) TB, defined as *Mycobacterium tuberculosis* strains resistant to at least isoniazid and rifampicin, and extensively drug-resistant (XDR) TB, defined as MDR TB strains additionally resistant to at least one fluoroquinolone and one second-line injectable agent (i.e. kanamycin, amikacin or capreomycin).[1–4] Due to the extent of resistance, treatment options for MDR and XDR TB are limited, and new, effective drugs are needed.

Linezolid, an oxazolidinone, may be an important option for the treatment of MDR and XDR TB. However, the current recommended duration of MDR TB treatment is ≥18–24 months and such prolonged use of linezolid is associated with numerous side effects.[5–7] Early studies investigating the use of linezolid to treat MDR TB administered a linezolid dose of 600 mg given twice daily, the dose approved by the United States Food and Drug Administration for the treatment of Gram-positive organisms. These studies reported rapid sterilization of *M. tuberculosis* cultures following the addition of the drug to anti-TB regimens, although myelosuppression and neurotoxicity were common and required discontinuation of linezolid in many cases.[8–10] Findings from later studies suggest that a linezolid dose of 600 mg given once daily effectively sterilizes *M. tuberculosis* cultures and is associated with a reduced incidence of myelosuppression and, in some cases, neurotoxicity.[11–15] Although there is evidence that this linezolid dose may decrease the overall incidence of adverse events, linezolid use was complicated by some degree of toxicity in all cohorts. Further, limited information was provided regarding management of adverse events.

We examined treatment outcomes, as well as incidence, management and predictors of adverse events among a

cohort of 16 MDR TB patients, including 10 patients with XDR TB, who were treated with linezolid as part of salvage regimens in New York City (NYC).

Methods

We retrospectively reviewed records of MDR TB patients who received treatment with linezolid for ≥1 month in NYC between January 2000 and December 2006. Patients were treated by physicians at NYC Department of Health and Mental Hygiene (DOHMH) chest clinics, private and public hospitals or clinics, or private medical providers. For all patients not directly treated by DOHMH providers, management and treatment recommendations were provided by one of three of the authors (F. D., S. S. M. or D. M. N.). Seven of the 16 patients were included in a previous case series published by a single NYC municipal hospital[10] (Patients 1, 2, 4, 7, 8, 15 and 16 in Table 1). We included these patients in this study in order to present the complete NYC experience of managing MDR TB patients with linezolid from a TB control programme perspective. Linezolid was administered as a component of individualized MDR TB treatment regimens after DOHMH consultants reviewed the clinical history of patients, including the resistance profile of *M. tuberculosis* isolates and prior anti-TB drug use. Linezolid and other anti-TB drugs were provided at no cost to the patient, in accordance with New York State Public Health Law.[16] Patients were monitored at least monthly for sputum culture status and occurrence of adverse events; monitoring included complete blood counts, liver function tests and vision tests.

Drug susceptibility testing (DST) was conducted at two reference laboratories; the NYC Public Health Laboratories and the New York State Wadsworth Center, Albany, NY, USA. DST was performed using the BACTEC MGIT 960 or radiometric BACTEC 460 systems (Becton Dickinson Microbiology Systems, Sparks, MD, USA) for first-line drugs (isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin) and with the agar proportions method for first- and second-line drugs [rifabutin, capreomycin, kanamycin, amikacin, a fluoroquinolone (usually ciprofloxacin or ofloxacin), ethionamide, cycloserine and *para*-aminosalicylic acid (PAS)]. Some isolates were sent to the National Jewish Medical Center (Denver, CO, USA) for additional DST, including for linezolid, amoxicillin/clavulanate and clofazimine. In 2003, DST for linezolid resistance became standard practice for all MDR TB patients who were being considered for linezolid therapy in NYC.

Using a standardized data abstraction form, information was obtained from the DOHMH TB registry, including demographics, bacteriology, DST, anatomical site of disease, initial chest radiograph result, directly observed therapy (DOT), treatment regimens and treatment outcome. In addition, medical records were reviewed from all providers who treated the patient for TB during the time period of linezolid administration to collect data on co-morbid conditions, non-TB medications, surgical intervention for TB, and occurrence and management of adverse events. Patients were encouraged to continue follow-up for 2 years after treatment completion; available data on sputum status during this follow-up period were collected from the TB registry. Relapse information was obtained by searching the TB registry to determine if any patients were later reported as a TB case in NYC at any time after TB treatment was stopped through 9 November 2009.

Sputum culture conversion was defined as two negative sputum cultures taken ≥1 month apart. Treatment completion was defined as ≥18 months of treatment that included ≥12 months following the last positive culture. Abnormal laboratory values or clinical symptoms and signs were clinically attributed to linezolid as determined by the treating physician's professional opinion and documented as such within the progress notes of the medical record. Time to occurrence of the adverse event was the number of weeks between the date the patient started linezolid and the date the adverse event was first documented in the record.

We performed bivariate analysis to investigate demographic and clinical factors associated with the occurrence of adverse events after starting linezolid, using Fisher's exact test for categorical variables and the Wilcoxon two-sample rank test for continuous variables. Statistical analysis was performed using SAS, version 9.2 (SAS Institute, Cary, NC, USA).

This study was approved by the Institutional Review Boards at the NYC DOHMH and at the CDC.

Results

Patient characteristics

From 2000 to 2006, 216 patients were treated for culture-confirmed MDR TB in NYC. Sixteen (7%) MDR TB patients, including 10 with XDR TB, received linezolid as part of individualized treatment regimens (Table 1). Twelve (75%) had at least one co-morbid condition, including three (19%) with HIV co-infection. Seven patients (44%) had surgical interventions to treat TB. DOHMH clinicians were the providers for the majority of TB care for nine (56%) patients. All patients were hospitalized or were on DOT for the first 6 months of MDR TB treatment and 14 (88%) were hospitalized or on DOT for the duration of therapy.

Initiation and duration of linezolid use

Patients' *M. tuberculosis* isolates were resistant to a median of 11 drugs (range: 7–16) and were treated for TB for a median of 5 months (range: 2–84) prior to starting linezolid (Figure 1 and Table 1). Patients were treated with linezolid for a median duration of 16 months (range 1–29) (Table 1). Linezolid was added to regimens containing a median of five other drugs (range: 1–6), including pyrazinamide ($n=6$, 38%), cycloserine ($n=11$, 69%), a fluoroquinolone ($n=12$, 75%), capreomycin ($n=8$, 50%), ethionamide ($n=9$, 56%), PAS ($n=5$, 31%) and clofazimine ($n=5$, 31%). Five (31%) patients were treated with inhaled interferon-γ (200 μg three times a week) and six (38%) were treated with a high dose of isoniazid (900 mg daily). Of note, Patient 10 was treated with first-line drugs for 15 months prior to culture confirmation of TB disease. A second-line regimen was started after XDR *M. tuberculosis* was isolated from a lower respiratory tract specimen and linezolid was added to the regimen 4 months later.

Treatment outcomes of MDR TB patients on linezolid

Eleven patients (69%) completed treatment and three (19%) died while on treatment. One patient had a relapse 6 months after treatment completion and died 2 weeks after relapse. TB treatment was discontinued in one patient (Patient 10) because of intolerance to anti-TB and HIV medications; the patient was monitored off-therapy for 7 months during which sputum specimens remained culture-negative for *M. tuberculosis* (see Table 1 and Figure 2). Seven of 10 patients with XDR TB completed treatment, and 0 of the 3 patients with HIV and XDR TB co-infection died during the study period.

Figure 2 presents a timeline of *M. tuberculosis* culture status for the 15 pulmonary MDR TB patients before and after linezolid was added to treatment regimens. All 11 patients with culture-positive sputum prior to starting linezolid converted a median of 29 days (range: 1–118) after starting linezolid. Two patients

Table 1. Demographic, clinical and treatment outcome information for 16 patients given linezolid as a part of MDR TB treatment regimens

Patient	Sex	Age (years)	Co-morbid conditions	Site of disease	Resistance profile prior to initiating LZD (in addition to INH, RIF, EMB and STR)	Concurrent medications to LZD	Surgery for TB disease	Months on TB drugs before LZD	Initial daily LZD dose (mg)	Total months on LZD	Discontinue LZD	Treatment outcome
1	F	43	diabetes, asthma, hypertension	pulmonary	PZA, CAP, KAN, AMK ETH, CIP, RFB, AMC	INH (900), ETH, CYC, PAS, CLO, IFN-G	yes	80	1200	25	no	completion, relapse, death
2	F	41	none	pulmonary	PZA, CAP, ETH, CIP, RFB, PAS	KAN, CYC, PAS, IFN-G	yes	84	1200	28	no	death
3	M	50	multiple sclerosis	pulmonary	PZA, RFB, PAS	INH (900), EMB, CAP, LVX	no	3	400	1	yes	completion
4	F	10	HIV, hepatitis B	pulmonary, pericardial, peritoneal	PZA, CAP, KAN, AMK, ETH, CIP, RFB, PAS, AMC	PZA, CAP, ETH, LVX, IPM, IFN-G	yes	2	800	27	no	completion
5	M	42	COPD	pulmonary	PZA, CAP, KAN, AMK, ETH, CIP, OFX, RFB, AMC	INH (900), CAP, CYC, PAS, CLO, IFN-G	yes	9	1200	29	yes	completion
6	F	68	diabetes, hypertension	pulmonary	PZA, RFB, PAS	INH (900), ETH, CYC, LVX	no	4	1200	4	no	death
7	F	27	none	pulmonary	PZA, CAP, KAN, AMK, ETH, CIP, LVX, OFX, RFB, PAS, AMC, CLO	INH (900), CAP, ETH, CYC, IFN-G	yes	5	1200	20	no	completion
8	F	49	diabetes, asthma, hepatitis C, multiple sclerosis, hypertension	pulmonary	PZA, CAP, KAN, AMK, RFB, PAS	PZA, CAP, ETH, LVX	no	2	600	8	yes	death
9	F	33	HIV, drug abuse	spinal	KAN, AMK, ETH, LVX, RFB	LVX	no	13	1200	7	no	completion
10	M	65	HIV	lymph node, pulmonary	CAP, KAN, ETH, CYC, CIP, RFB, PAS, AMC	INH (900), EMB, PZA, RFB, GAT	no	19	1200	2	no	monitor off therapy
11	M	25	COPD	pulmonary	PZA, ETH, CYC, RFB, PAS	PZA, AMK, ETH, CYC, MXF	yes	10	1200	4	yes	completion
12	F	38	diabetes, hypertension, renal failure	pulmonary	KAN, AMK, ETH, CYC, CIP, RFB, PAS, AMC	PZA, CAP, CYC, LVX, PAS, CLO	no	4	600	25	no	completion

Continued

Table 1. *Continued*

Patient	Sex	Age (years)	Co-morbid conditions	Site of disease	Resistance profile prior to initiating LZD (in addition to INH, RIF, EMB and STR)	Concurrent medications to LZD	Surgery for TB disease	Months on TB drugs before LZD	Initial daily LZD dose (mg)	Total months on LZD	Discontinue LZD	Treatment outcome
13	M	20	hepatitis B	pulmonary	PZA, CAP, KAN, AMK, CYC, CIP, LVX, OFX, RFB, PAS, AMC	PZA, CAP, ETH, CYC, LVX, CLO	no	3	1200	4	yes	completion
14	F	29	none	pulmonary	PZA, CAP, KAN, AMK	ETH, CYC, LVX, PAS	no	5	600	13	no	completion[a]
15	M	37	hepatitis B	pulmonary	PZA, CAP, KAN, AMK, CYC, RFB, PAS, AMC	ETH, CYC, MXF	no	6	1200	22	no	completion
16	F	20	none	pulmonary	PZA, KAN, ETH, CIP, RFB, PAS, AMC	EMB, CAP, CYC, MXF, CLO	yes	2	1200	27	no	completion

LZD, linezolid; INH, isoniazid; INH (900), 900 mg high dose isoniazid; RIF, rifampicin; EMB, ethambutol; PZA, pyrazinamide; STR, streptomycin; CAP, capreomycin; KAN, kanamycin; AMK, amikacin; ETH, ethionamide; CYC, cycloserine; CIP, ciprofloxacin; LVX, levofloxacin; OFX, ofloxacin; RFB, rifabutin; PAS, *para*-aminosalicylic acid; AMC, amoxicillin/clavulanate; CLO, clofazimine; MXF, moxifloxacin; GAT, gatifloxacin; IPM, imipenem; IFN-G, recombinant human interferon-γ; COPD, chronic obstructive pulmonary disease; M, male; F, female.
[a]Completed MDR TB treatment outside of NYC jurisdiction.

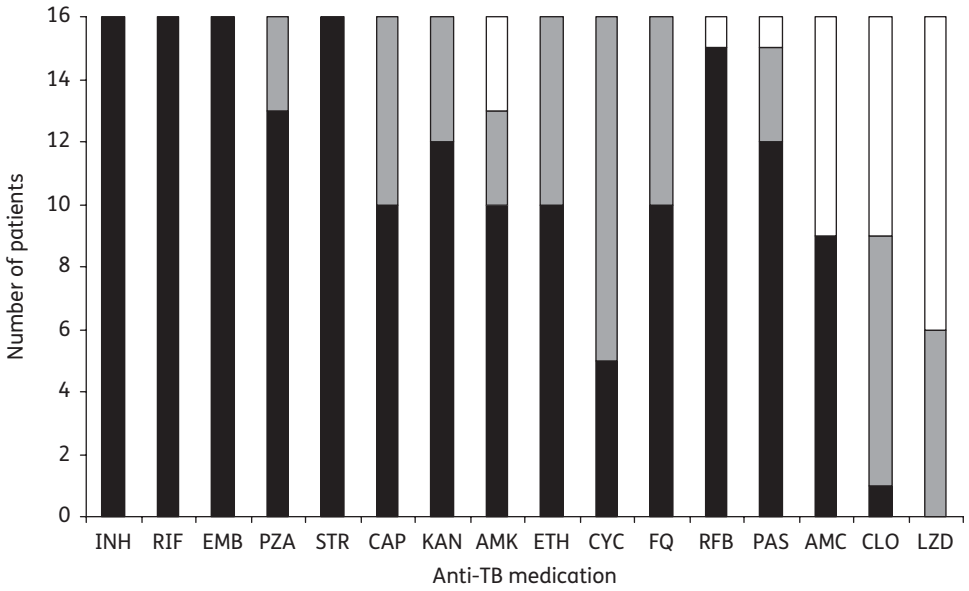

Figure 1. Drug resistance profile of *M. tuberculosis* isolates obtained from 16 patients with MDR TB before linezolid was added to individualized treatment regimens. Grey, susceptible; black, resistant; white, not tested. INH, isoniazid; RIF, rifampicin; EMB, ethambutol; PZA, pyrazinamide; STR, streptomycin; CAP, capreomycin; KAN, kanamycin; AMK, amikacin; ETH, ethionamide; CYC, cycloserine; FQ, fluoroquinolone; RFB, rifabutin; PAS, *para*-aminosalicylic acid; AMC, amoxicillin/clavulanate; CLO, clofazimine; LZD, linezolid.

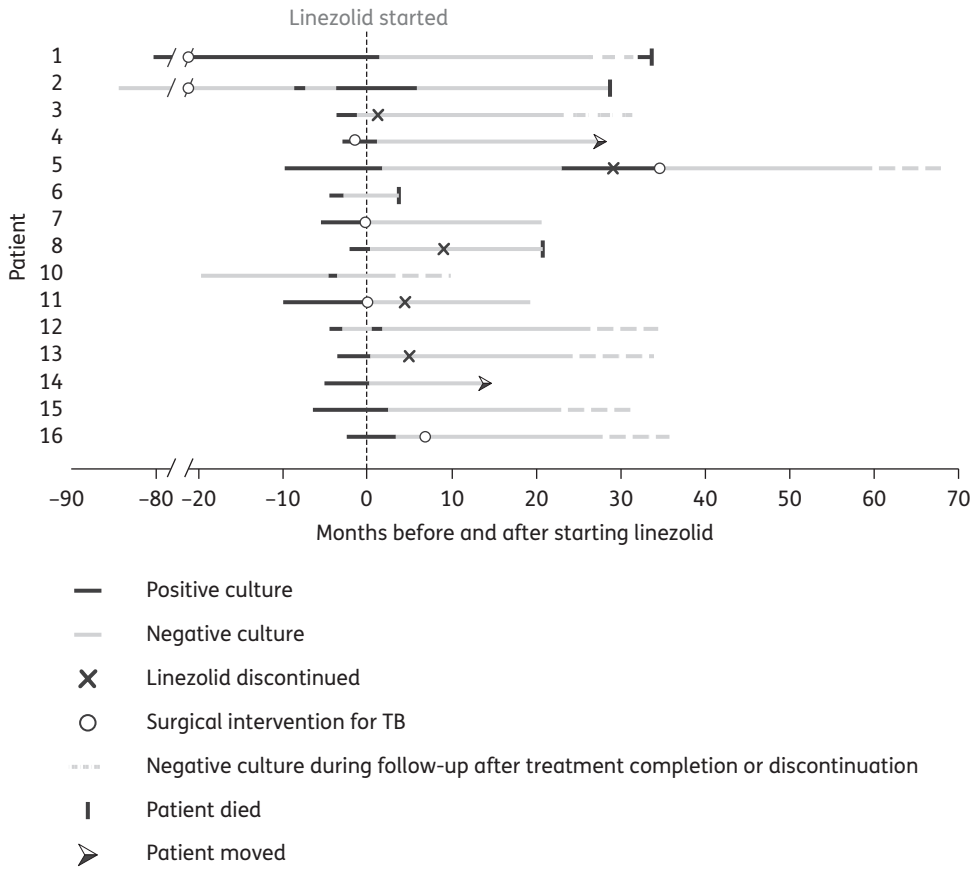

Figure 2. Mycobacterial culture status before and after starting linezolid among 15 patients with pulmonary MDR TB. Time 0=time linezolid was added to the regimen. Patient 9 omitted due to extrapulmonary (spinal) TB disease with only one positive culture.

(Patients 7 and 11) had pulmonary surgical intervention for TB at approximately the same time linezolid was added to the regimen; both had culture conversion immediately afterward.

Incidence and management of adverse events

All 16 patients had adverse events after starting linezolid that were categorized as haematological ($n=13$, 81%), gastrointestinal (GI; $n=13$, 81%) or neurological ($n=7$, 44%) (Table 2). Management of adverse events consisted of a combination of strategies that are outlined in Table 2.

Haematological adverse events occurred in 13 (81%) patients, including 8 of the 11 adult patients who were administered a 600 mg twice daily linezolid dose and in all 4 adult patients who took a 600 or 400 mg once daily dose. Nine (69%) of the 13 patients with haematological events had linezolid temporarily suspended for a median of 16 days (range: 5–146), although events recurred in 6 patients following reintroduction of the drug. Six (46%) of the 13 patients had the linezolid dose reduced to manage haematological events; events recurred in 3 patients when the dose was increased and events did not recur in 3 patients who maintained the reduced dose for the duration of therapy. Adverse events in 8 (62%) of the 13 patients were managed with combinations of epoetin alpha administration, blood transfusion, folic acid and iron supplementation for anaemia, and filgrastim for leucopenia. Linezolid was discontinued in 3 (23%) of the 13 patients with haematological events, including 1 patient with both anaemia and thrombocytopenia, 1 patient with both thrombocytopenia and leucopenia, and 1 patient with anaemia (who also had peripheral neuropathy). Ultimately, haematological effects resolved for 5 (38%) of the 13 patients.

GI adverse events occurred in 13 (81%) patients, including 8 of the 11 adult patients who were administered a 600 mg twice daily linezolid dose and in all 4 adult patients who took a 600 or 400 mg once daily dose. Eight (62%) of the 13 patients with GI events required temporary suspension of linezolid for a median of 6 days (range: 3–37) and although GI problems recurred in 5 patients, these events ultimately resolved for 4 patients. In 9 (69%) of the 13 patients, GI events were effectively managed by treating symptoms with anti-emetic or antidiarrhoeal medication. Overall, GI events resolved for 12 of 13 (92%) patients. One patient (Patient 10) with HIV co-infection had lactic acidosis that was attributed to antiretroviral therapy.

Neurotoxicity occurred in 7 (44%) patients, including 6 (55%) of the 11 adult patients who took a linezolid dose of 600 mg twice daily. To manage neurotoxicity, linezolid was temporarily suspended for 7 days in one patient, two had the linezolid dose reduced for the duration of therapy and three had their symptoms managed by administration of gabapentin or increasing vitamin B6 intake. Discontinuation of linezolid was required for three (43%) of the seven patients with neurotoxicity. One patient had both optic and peripheral neuropathy, and while optic neuropathy resolved with discontinuation of linezolid, peripheral neuropathy did not resolve for this patient or any other patient with peripheral neuropathy.

Risk factors for adverse events

More males developed leucopenia (four versus one, $P=0.04$) and peripheral neuropathy (five versus two, $P=0.035$) than females (data not shown). After excluding the 10-year-old patient, those who developed thrombocytopenia were older (median age 49 years, range: 37–68) than patients who did not (median: 29 years, range: 20–43, $P=0.04$). One patient (Patient 11) reported alcohol abuse, and developed both peripheral and optic neuropathy. Other demographic and behavioural characteristics were not associated with adverse events.

Co-morbid conditions were common. Two of three patients co-infected with HIV developed both pancytopenia and peripheral neuropathy. All three patients with hepatitis B co-infection developed peripheral neuropathy and anaemia. Three of the four patients with co-morbid diabetes had incident anaemia and thrombocytopenia. Of note, none of the four patients with diabetes had incident peripheral neuropathy. There was not a significant association between co-morbid conditions and the occurrence of adverse events.

Acquired resistance to linezolid

Patient 5 maintained good treatment adherence on DOT and had negative sputum culture results 1 month after linezolid was added to the regimen. After 11 months of sustained culture sterilization, the patient began self-administered treatment and was non-adherent. Ten months later, sputum culture results were positive and DST revealed resistance to linezolid. Linezolid was discontinued and the patient continued anti-TB treatment with an adjusted regimen. The patient underwent a left lower lobectomy, had negative sputum culture results and completed therapy ∼2 years later (Figure 2).

Discussion

Despite high rates of drug resistance and co-morbidities in this cohort of MDR TB patients, our results support other studies that document favourable intermediate[11,13,15] and long-term outcomes for MDR TB patients treated with linezolid.[8–10,12,14,17] All patients who had culture-positive sputa prior to starting linezolid had culture conversion a median of 1 month after the drug was added, suggesting that linezolid contributed to favourable outcomes. However, three patients who completed anti-TB treatment had to discontinue linezolid after <5 months of taking the drug, making it difficult to determine what role linezolid played in the outcomes observed in these patients. Further, two patients had pulmonary surgical resection at the same time that linezolid was added to the regimen; for these patients, it is unknown if sputum culture conversion occurred because of the addition of linezolid or because of surgery. Three patients in our study had XDR TB/HIV co-infection, a combination documented to have high fatality rates.[4] Despite poor prognoses, two XDR/HIV co-infected patients completed treatment with a linezolid-containing regimen. Although all therapy was discontinued in the remaining co-infected patient, no relapse was detected during 7 months of available follow-up.

All patients in this study were either hospitalized or received DOT during the first 6 months of therapy and the majority continued DOT until completion. The importance of DOT is underscored by the experience of one patient who relapsed with linezolid-resistant TB after non-adherence to a self-administered treatment with a linezolid-containing regimen. Monitoring patient therapy throughout the course of treatment is essential to

Table 2. Summary measures of the occurrence and management of adverse effects after starting linezolid among 16 patients with MDR TB

	Incidence of adverse events			Management of adverse events[a]						
Adverse event	reporting effect (*n*, %)	clinically attributed to LZD (*n*)	weeks on LZD prior to occurrence (median, range)	temporarily suspend LZD (*n*, %)	duration of suspension in days (median, range)	discontinue LZD (*n*, %)	reduce LZD dose (*n*, %)	duration of reduction in days (median, range)	manage symptoms (*n*, %)	Resolution of adverse event (*n*, %)[b,c]
Any adverse event	16 (100%)	13	3 (1–16)	14 (88%)	12 (4–146)	5 (31%)	7 (44%)	182 (48–708)	13 (81%)	5 (31%)[d]
Haematological	13 (81%)	10	5 (1–11)	9 (69%)	16 (5–146)	3 (23%)	6 (46%)	133 (17–646)	8 (62%)	5 (38%)
anaemia	11 (69%)	8	7 (1–11)	8	19 (5–146)	2	6	133 (17–646)	8	4 (36%)
thrombocytopenia	8 (50%)[e]	5	5 (2–22)	5	18 (7–146)	2	2	332 (17–636)	0	5 (63%)
leucopenia	5 (31%)	2	7 (1–10)	2	22 (7–37)	1	2	332 (17–636)	2	2 (40%)
pancytopenia	3 (19%)	2	7 (2–10)	1	7 (NA)	0	2	332 (17–636)	2	1 (33%)
Gastrointestinal (GI)	13 (81%)	4	8 (1–57)	8 (62%)	6 (3–37)	0	0	—	9 (69%)	12 (92%)
GI disturbance	13 (81%)	4	8 (1–57)	8	6 (3–37)	0	0	—	10	12 (92%)
lactic acidosis	1 (6%)	0	10 (NA)	1	7 (NA)	0	0	—	0	0 (0%)
Neurological	7 (44%)	5	16 (10–111)	1 (14%)	7 (NA)	3 (43%)	2 (29%)	622 (536–708)	3 (43%)	0 (0%)
peripheral neuropathy	7 (44%)	5	16 (10–111)	1	7 (NA)	2	2	622 (536–708)	3	0 (0%)
optic neuropathy	1 (6%)	1	18 (NA)	0	—	1	0	—	0	1 (100%)
Dermatological										
rash	5 (31%)	0	4 (1–13)	0	—	0	0	—	4	5 (100%)

LZD, linezolid; NA, not applicable.
[a]Management includes any combination of the listed management methods; categories are not mutually exclusive.
[b]Percentages reflect the proportion of patients that had the adverse event.
[c]Resolution of adverse events is only documented for the time span covered in the medical record review, i.e. the time patients were taking linezolid.
[d]Number and percentage of patients for whom all adverse events resolved.
[e]Includes one patient who developed thrombocytopenia while outside NYC jurisdiction and was resolved with temporary suspension of LZD for 10 days.

achieving favourable treatment outcomes and to maintaining the dwindling drug arsenal for treating highly resistant strains of TB.[18,19]

High rates of myelosuppression and neurotoxicity were limiting factors for linezolid use in our cohort, as has been reported by others.[8,9,13,14] It is important to note that patients in our cohort had high rates of co-morbidities that may have increased their risk of adverse events. In addition, all patients in our cohort were on multidrug anti-TB regimens that included other medications that may have caused or worsened adverse events. However, we note that the treating clinician's judgement did indicate that linezolid was most likely the cause of adverse events in 10 of the 13 patients who had myelosuppression and in 5 of the 7 patients who experienced neurotoxicity. Despite rigorous management, linezolid was discontinued in five patients. Myelosuppression was more responsive to clinical management than was neuropathy. Myelosuppression resolved with dose reduction and recurred in patients who resumed the full dose. Neuropathy was not responsive to dose adjustment, temporary suspension or symptom management in our cohort. Neuropathy occurred a median of 16 weeks (range: 10–111) after starting linezolid, suggesting that neuropathy is associated with prolonged use of the drug and that a shorter duration of linezolid administration may reduce the incidence of neuropathy. However, it is unknown whether a shorter duration of linezolid use would impact the long-term efficacy of the drug.

Studies investigating linezolid at a lower dose (600 or 300 mg once daily) report high rates of mycobacterial culture conversion and a reduced incidence of adverse events.[11,13–15] Notably, a recent MDR TB case series in California reported high efficacy and low rates of myelosuppression and neurotoxicity among patients treated with a 600 mg once daily dose of linezolid coupled with vitamin B6 administration.[12] In contrast, all four patients in our cohort who began treatment with a 600 mg once daily linezolid dose or lower experienced myelosuppression and two ultimately required discontinuation of linezolid. We note that patients in the Californian cohort were treated with linezolid earlier in the MDR TB treatment while most patients in our cohort were treated with linezolid later in treatment as a component of salvage regimens. Further, patients in our cohort had *M. tuberculosis* isolates that were resistant to a large number of anti-TB drugs (median 11) and had a higher rate of XDR TB than the patients in the Californian case series (63% versus 10%). Despite these factors, the Californian cohort reported treatment completion rates comparable to those we report in our cohort. Ultimately, the differing characteristics in the two groups of patients and the small numbers in both our study and the Californian study make it difficult to draw comparisons or conclusions regarding efficacy or decreased toxicity of various doses of linezolid. It remains unclear whether a full course of treatment with a lower linezolid dose would contribute to favourable long-term outcomes.

Our study conclusions are limited by the small number of patients and the retrospective nature of our analysis. The small sample size limited our ability to examine risk factors for adverse events; however, we do note that older age increased the risk of thrombocytopenia, and male sex was associated with a higher incidence of peripheral neuropathy and leucopenia. Also, although the review of public health records spanned the entire length of MDR TB treatment, the medical record review was limited to the time period of linezolid administration; thus, we had incomplete data on the resolution of adverse events. Resolution of adverse events may have occurred after linezolid was stopped, as has been documented by others for myelosuppression,[6,8,20,21] though not for neurotoxicity.[5,8,13,21] Despite these limitations, our study adds important knowledge on the subject of linezolid for the treatment of MDR TB. Treating physicians and DOHMH consultants closely monitored all patients and provided prompt intervention for adverse events.

Our results support the growing evidence that linezolid has efficacy against MDR TB. However, the current recommended duration of therapy contributes to high toxicity rates. Additional studies are needed to investigate whether a lower linezolid dose or shorter duration of administration may minimize toxicity and still be effective. Overall, our results suggest that, when employed in conjunction with other strategies such as sound DOT practices, surgical intervention and individualized treatment regimens designed according to drug susceptibility results, linezolid may be an effective treatment option for patients with severely resistant TB strains, although all cases should be monitored closely for occurrence of serious side effects.

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Transparency declarations

None to declare.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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