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Linezolid Exposure Is Associated with Cytopenias in Patients Treated for Multidrug-Resistant Tuberculosis

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ABSTRACT Although linezolid is effective for multidrug-resistant TB (MDR-TB) tuberculosis treatment, it is associated with cytopenias after 4 weeks of administration. Data on toxicities with long-term use of linezolid and drug pharmacodynamics in MDR-TB treatment are limited, and concerns about toxicity present barriers to wider implementation. This was a secondary analysis of a prospective cohort study of patients treated for MDR-TB in the country of Georgia from 2015 to 2017. Intensive blood sampling 4 to 6 weeks after treatment initiation with linezolid 600 mg daily was performed for pharmacokinetic (PK) analysis, including linezolid trough concentration (C_{min}) and area under the curve from 0 to 24 hours (AUC_{0-24}). Linezolid exposure was defined using literature-reported thresholds. Cytopenias were defined using an NIH adverse event (AE) scale. Logistic regression was used to evaluate the relationship between linezolid exposure and cytopenias. Among 76 patients receiving linezolid in their baseline treatment regimen and who had PK data available, cytopenia AEs occurred in 30 (39.5%) for an incidence rate of 46 per 100 person-years. The median duration of linezolid therapy was 526 days. No patients required dose reduction or interruption due to cytopenias. Median linezolid C_{min} was 0.235 mg/L (interquartile range [IQR], 0.069 to 0.529), and median AUC_{0-24} was 89.6 mg·h/L (IQR, 69.2 to 116.2). Cytopenias were associated with linezolid PK parameters ($C_{min} > 2$ mg/L and $AUC_{0-24} > 160$ mg·h/L). Cytopenias occurred frequently with long-term use of linezolid 600 mg/day and were associated with PK parameters but did not result in the need for treatment interruption in the management of a cohort of patients with MDR-TB.

KEYWORDS *Mycobacterium tuberculosis*, adverse drug effects, cytopenia, linezolid

Tuberculosis (TB) remains a major global health problem, with an estimated 10 million incident cases of TB and 1.5 million deaths due to TB in 2020 and increasing global mortality for the first time in over 20 years (1). Multidrug-resistant TB (MDR-TB) is a major challenge to global TB control efforts and to ending the TB epidemic (1, 2). The development of novel anti-TB drugs and repurposing of existing drugs, such as linezolid, to treat MDR-TB have improved outcomes and shortened treatment regimens from up to 2 years to 6 to 12 months (3–6). Understanding how to best use these new and repurposed drugs is essential for safe and effective treatment of MDR-TB.

Linezolid is an oxazolidinone antibiotic with activity against *Mycobacterium tuberculosis* that is now included in the WHO DR-TB treatment guidelines as a "group A" drug for

MDR-TB treatment to be included in all regimens unless contraindicated (7, 8). However, these guidelines still advise caution with prolonged use of linezolid, as therapy >4 weeks has been associated with adverse effects such as cytopenias and neuropathy (7). Development of cytopenias is related to total linezolid exposure in both a time- and dose-dependent fashion, though the mechanism is not well-defined and the reported duration of linezolid therapy preceding the development of cytopenias is variable and as short as 5 to 14 days (7, 9, 10). While the current recommended treatment duration for MDR-TB is 6 to 18 months, data on long-term use of linezolid and development of toxicities remain limited, particularly in the treatment of TB (11). Recent studies suggest that linezolid-associated adverse events (AEs) occur frequently in patients treated for TB, with 48% of patients in the Nix-TB clinical trial developing cytopenias and 85% requiring linezolid interruption or dose reduction due to an AE (5). Notably, linezolid was dosed at 1,200 mg/day in this trial, while the standard dose per WHO guidelines and used in programmatic settings via national TB programs (NTP) is 600 mg/day (8). To address the safety of this standard dose, we previously conducted a retrospective analysis of patients treated for MDR-TB in the country of Georgia, and it suggested that linezolid dosed at 600 mg/day is tolerable (12). Similar to other countries in the region, Georgia has one of the highest rates of MDR-TB in the world. In 2015, the Georgian NTP implemented new and repurposed drugs, including linezolid, into routine programmatic use for the treatment of MDR-TB (1, 13). Pharmacokinetic/pharmacodynamic data may complement prior clinical data to optimize linezolid use for TB (11).

Pharmacokinetic (PK) parameters that have been proposed as informing linezolid safety include the trough or minimum serum concentration (C_{min}) and area under the curve (AUC). While PK parameters for efficacy in TB treatment are not yet defined, a C_{min} threshold of >2 mg/L for linezolid efficacy in Gram-positive infections in humans has been proposed based on available clinical data (14, 15). However, values above 2 mg/L have also been associated with mitochondrial protein synthesis toxicity, which is a potential mechanism for cytopenias (16–18). Pharmacologic data for linezolid in the treatment of MDR-TB remain limited. PK modeling utilizing patient data from several settings, including Georgia, suggests that the 600-mg/day dose may maximize efficacy while minimizing toxicity compared to 900-mg or 1,200-mg daily dosing, assuming a low MIC (19). The goal of the present study was to incorporate PK data with clinical outcome data from an existing cohort of patients treated for MDR-TB in Georgia to assess the development of cytopenias with long-term use of linezolid to support safe and effective treatment of MDR-TB.

RESULTS

Among a total of 156 patients initiating therapy for MDR-TB, 100 patients provided written informed consent and were enrolled in the study (Fig. 1). Clinical characteristics and outcomes for the parent cohort have been described; treatment outcomes were favorable in 72 (72%), with 91 (91%) achieving sputum culture conversion (20). Linezolid was included in the initial regimen for 80 patients (at a dose of 600 mg daily); 76 had blood drawn for PK evaluation and were included in the primary analysis. The median age of this group was 36.8 years (interquartile range [IQR], 27.7 to 49.9), and most (77%) were male (Table 1). Tobacco use (48.7%) and alcohol use (30.3%) were common. Medical records indicated diabetes mellitus was present in 10 (13.2%) participants, anti-hepatitis C virus (HCV) antibodies in 19 (25.0%), and human immunodeficiency virus (HIV) infection in 2 (2.6%). Clinical outcomes for patients in the primary analysis were favorable overall, with 53/76 (69.7%) cured or completing treatment (Table 1). Patients received linezolid for a median of 526 days (IQR, 305 to 607). The median baseline complete blood count (CBC) values were within normal limits, with white blood cell (WBC) count of $9.4 \times 10^3/\mu L$ (IQR, 7.5 to 11.0); hemoglobin, 12.5 g/dL (IQR, 11.3 to 14.0); and platelets, $373 \times 10^3/\mu L$ (IQR, 306 to 489) (Table 1). Baseline values were within the AE range for anemia in 21 patients and for thrombocytopenia in 2 patients. The median number of follow-up CBC collections was 8 (IQR, 5 to 12). From
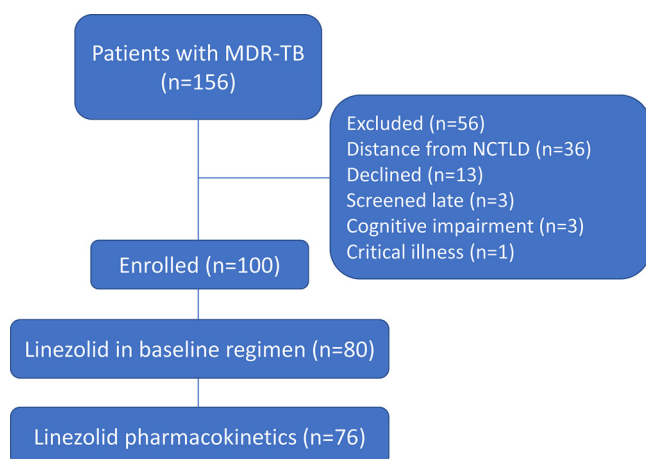
FIG 1 Study population of patients with MDR-TB initiating treatment at the NCTLD from December 2015 to May 2017. NCTLD, National Center for Tuberculosis and Lung Diseases; MDR-TB, multidrug-resistant TB; TB, tuberculosis.

baseline to the last recorded CBC value in follow-up, the mean change in hemoglobin was -1.2 g/dL (range, -5.1 to 1.7) and in platelets was $115 \times 10^3/\mu$L (range, -71 to 356). For PK parameters, the median linezolid C_{min} was 0.235 mg/L (IQR, 0.069 to 0.529), median maximum serum concentration (C_{max}) was 10.24 mg/L (IQR, 7.77 to 12.62), and median AUC from 0 to 24 h (AUC_{0-24}) was 89.6 mg·h/L (IQR, 69.2 to 116.2). Among the 76 patients, 7 (9.2%) had linezolid C_{min} above the 2-mg/L efficacy/mitochondrial toxicity threshold, and 0 were above the 7-mg/L thrombocytopenia threshold. For linezolid AUC_{0-24}, 10 (13.2%) had values above the 160-mg·h/L efficacy threshold, and 1 (1.3%) had a value above the 280-mg·h/L toxicity threshold.

Incident cytopenias. Overall, 30 (39.5%) of 76 study participants developed a cytopenia AE (Table 2). An AE for individual CBC parameters occurred in one participant (1.3%) for leukopenia (white blood cells $< 2.5 \times 10^3/\text{mm}^3$), in 23 (30.3%) for anemia (hemoglobin < 11.0 g/dL), and in 11 (14.5%) for thrombocytopenia (platelets $< 125 \times 10^3/\mu$L). Most of these were grade 1 (23, 76.7%) or grade 2 (11, 36.7%) AEs. There was one grade 3 AE for any cytopenia (thrombocytopenia $< 50 \times 10^3/\mu$L) and no grade 4 AE for any parameter. The incidence rate of any cytopenia AE was 46 per 100 person-years, including 35 per 100 person-years for anemia and 16 per 100 person-years for thrombocytopenia. However, only four study participants stopped linezolid due to any AE, and these were not for cytopenias but for neuropathy ($n = 2$) and hepatotoxicity ($n = 2$). No participants required dose reduction. Incident cytopenias occurred at a median of 4 months (IQR, 3 to 7) for any cytopenia, 4 months (IQR, 3 to 6) for anemia, and 11 months (IQR, 5 to 13) for thrombocytopenia (see Fig. S1 in the supplemental material). Among the 23 participants with anemia, 22 had recorded resolution at a median of 2 months (range, 1 to 6 months). Among the 11 participants with thrombocytopenia, 9 had recorded resolution at a median of 1 month (range, 1 to 2 months). All cytopenias occurred during the linezolid treatment course.

Linezolid exposure and cytopenias. Logistic regression modeling suggests that linezolid pharmacokinetic exposure as defined by C_{min} and AUC_{0-24} thresholds is associated with development of cytopenias when evaluating the three outcomes of any cytopenia, anemia, and thrombocytopenia (Table 3). Those with C_{min} values of >2 mg/L had higher odds of developing any cytopenia than those with C_{min} values of ≤ 2 mg/L (odds ratio [OR], 4.40; 95% confidence interval [CI], 0.79 to 24.4). Those with C_{min} values of >2 mg/L also had higher odds of developing anemia than those with C_{min} values of ≤ 2 mg/L (OR, 3.51; 95% CI, 0.72 to 17.2). For both outcomes, these associations are somewhat attenuated in the adjusted model, and similar, though smaller, magnitude associations are shown using linezolid AUC_{0-24} as the exposure (Table 3). Those study subjects with C_{min} values of >2 mg/L were also at higher risk of developing thrombocytopenia than those with C_{min} values of ≤ 2 mg/L (adjusted OR, 5.64; 95% CI, 1.01 to 31.4).

TABLE 1 Characteristics of patients ($n = 76$) with MDR-TB who were initiating treatment with linezolid-containing regimens[a]

Characteristic	Value
Age (median [IQR] [yrs])	36.8 (27.7–49.9)
Body mass index (median [IQR] [kg/m^2])	19.9 (18.4–22.4)
No. (%) male	59 (77.6)
Any tobacco use[e] (no. [%])	37 (48.7)
More than 1 pack per day	19 (25.0)
Any alcohol use[e] (no. [%])	23 (30.3)
Heavy[b]	8 (10.5)
Diabetes mellitus (no. [%])	10 (13.2)
HIV infection (no. [%])	2 (2.6)
Hepatitis C antibody positive (no. [%])	19 (25.0)
Case definitions (no. [%])	
New	34 (44.7)
Relapse	15 (19.7)
After loss to follow-up	10 (13.2)
After failure	10 (13.2)
Other	7 (9.2)
Pulmonary disease only (no. [%])	75 (98.7)
Cavitary disease (no. [%])	47 (61.8)
AFB sputum smear positive[c] (no. [%])	54 (71.1)
Extensive drug resistance (no. [%])	16 (21.1)
Baseline laboratory values (median [IQR])	
White blood cells ($\times 10^3/\mu$L)	9.4 (7.5–11.0)
Hemoglobin (g/dL)	12.5 (11.3–14.0)
Platelets ($\times 10^3/\mu$L)	373 (306–488.5)
Creatinine (μmol/L)	71 (61–84)
Treatment characteristics (median [IQR])	
SLD treatment duration (days)	609 (461–622)
New drug[d] treatment duration (days)	532 (348–608)
Linezolid duration (days)	526 (305–607)
Treatment duration prior to linezolid start (days)	27.5 (0–112)
Linezolid stop prior to completion (no. [%])	
Adverse event	4 (5.3)
Poor outcome	13 (17.1)
Clinical outcomes (no. [%])	
Favorable outcome	53 (69.7)
Any acquired drug resistance	12 (16.2)

[a]MDR-TB, multidrug-resistant TB; TB, tuberculosis; PK, pharmacokinetic; IQR, interquartile range; HIV, human immunodeficiency virus; SLD, second-line drugs.
[b]"Heavy" represents >15 drinks per week for men and >8 drinks per week for women.
[c]At time of new drug initiation.
[d]New anti-TB drugs include bedaquiline, linezolid, clofazimine, and delamanid.
[e]Reported within 12 weeks of diagnosis.

Linezolid exposure and grade of cytopenias. Ordinal logistic regression modeling suggests that linezolid pharmacokinetic exposure has an exposure-response relationship with grade of cytopenia AE for thrombocytopenia and anemia. Patients with C_{min} values of >2 mg/L had higher odds of higher-grade thrombocytopenia AEs than those with C_{min} values of ≤2 mg/L (OR, 5.70; 95% CI, 1.11 to 29.2), with a similar association after adjusting for age and gender (adjusted OR [aOR], 5.95; 95% CI, 1.11 to 32.1) (Table 4). Using tertiles of C_{min} as exposure categories, there appears to be an exposure-response relationship, as the corrected OR (cOR) for higher-grade thrombocytopenia among patients with C_{min} values of >0.35 mg/L compared to those with C_{min} ≤0.12 mg/L was 3.76 (95% CI, 0.68 to 20.8), while among those with C_{min} values of >0.12 to 0.35 mg/L,

TABLE 2 Cytopenia adverse events among patients with MDR-TB initiating treatment with linezolid-containing regimens[a]

Adverse event	Data (no. [%]) for				Incidence rate of any event (per 100 person-yrs)
	Any event (n = 76)	Grade 1	Grade 2	Grade 3	
Any adverse event	30 (39.5)				46
Leukopenia	1 (1.3)	1 (1.3)			
Anemia	23 (30.3)	14 (18.4)	9 (11.8)		35
Thrombocytopenia	11 (14.5)	8 (10.5)	2 (2.6)	1 (1.3)	16

[a]Adverse events were defined according to the NIH Division of AIDS (DAIDS) grading table. There were no grade 4 adverse events.

the cOR was 1.55 (95% CI, 0.23 to 10.4). A similar association is seen after adjusting for age and gender. The odds of higher-grade thrombocytopenia and are also greater among those with higher AUC_{0-24} values than lower AUC_{0-24} values.

Study participants with MDR-TB on linezolid who had C_{min} values of >2 mg/L had much higher odds of developing higher-grade anemia AE than those with C_{min} values of ≤2 mg/L (OR, 13.33; 95% CI, 2.30 to 77.2) (Table 5). There is also an exposure-response relationship, as the OR for higher-grade anemia among patients with C_{min} values of >0.35 mg/L compared to those with C_{min} values of ≤0.12 mg/L was 2.52 (95% CI, 0.79 to 8.04), while among those with C_{min} values of >0.12 to 0.35 mg/L, the OR was 0.74 (0.20 to 2.77). A similar association is seen after adjusting for age and gender. Using AUC_{0-24} categories of exposure, the odds of higher-grade anemia among patients with AUC_{0-24} values of >160 mg·h/L were 12.0 times the odds among those with AUC_{0-24} values of ≤160 mg·h/L (95% CI, 2.31 to 59.8). This association is attenuated by adjustment for age and gender (aOR, 8.74; 95% CI, 1.58 to 48.3). As for C_{min}, there appears to be an exposure-response relationship between higher AUC_{0-24} and higher-grade anemia.

DISCUSSION

Among a cohort of patients with MDR-TB who received linezolid at 600 mg once daily as part of their TB treatment regimen, we found that cytopenia adverse events

TABLE 3 Logistic regression analysis of linezolid exposure and cytopenia adverse events among patients with MDR-TB (n = 76)[a]

Outcome	No. of patients/total no. of patients (%)	cOR (95% CI)	aOR[b] (95% CI)
Any cytopenia AE	30 (39.5)		
C_{min} > 2 mg/L	5/7 (71.4)	4.40 (0.79–24.4)	3.84 (0.67–22.1)
C_{min} ≤ 2 mg/L	25/69 (36.2)	Reference	Reference
AUC_{0-24} > 160 mg·h/L	6/10 (60.0)	2.63 (0.67–10.2)	2.05 (0.49–8.58)
AUC_{0-24} ≤ 160 mg·h/L	24/66 (36.4)	Reference	Reference
Thrombocytopenia AE	11 (14.5)		
C_{min} > 2 mg/L	3/7 (42.9)	**5.72 (1.08–30.3)**	**5.64 (1.01–31.4)**
C_{min} ≤ 2 mg/L	8/69 (11.6)	Reference	Reference
AUC_{0-24} > 160 mg·h/L	3/10 (30.0)	3.11 (0.67–14.5)	3.24 (0.63–16.7)
AUC_{0-24} ≤ 160 mg·h/L	8/66 (12.1)	Reference	Reference
Anemia AE	23 (30.3)		
C_{min} > 2 mg/L	4/7 (57.1)	3.51 (0.72–17.2)	3.01 (0.58–15.7)
C_{min} ≤ 2 mg/L	19/69 (27.5)	Reference	Reference
AUC_{0-24} > 160 mg·h/L	5/10 (50.0)	2.67 (0.69–10.3)	1.88 (0.44–7.98)
AUC_{0-24} ≤ 160 mg·h/L	18/66 (27.3)	Reference	Reference

[a]Bold denotes confidence intervals that exclude the null value. NCTLD, National Center for Tuberculosis and Lung Diseases; MDR-TB, multidrug-resistant TB; TB, tuberculosis; AE, adverse event; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval.
[b]Adjusted for age and gender.

TABLE 4 Ordinal logistic regression analysis of linezolid exposure and degree of thrombocytopenia among patients with MDR-TB ($n = 76$)[a]

Measure	No. of patients/total no. of patients (%) with AE grade of:			Data for higher-grade thrombocytopenia (95% CI)	
	None	1	2–3	cOR	aOR[b]
Linezolid C_{min} (mg/L)	65 (85.5)	8 (10.5)	3 (3.9)		
>2	4/7 (57.1)	2/7 (28.6)	1/7 (14.3)	**5.70 (1.11–29.2)**	**5.95 (1.11–32.1)**
≤2	61/69 (88.4)	6/69 (8.7)	2/69 (2.9)	Reference	Reference
>0.35	20/26 (76.9)	3/26 (11.5)	3/26 (11.5)	3.76 (0.68–20.8)	4.11 (0.71–23.9)
>0.12–0.35	22/25 (88.0)	3/25 (12.0)		1.55 (0.23–10.4)	1.50 (0.22–10.1)
≤0.12	23/25 (92.0)	2/25 (8.0)		Reference	Reference
Linezolid AUC_{0-24} (mg·h/L)					
>160	7/10 (70.0)	2/10 (20.0)	1/10 (10.0)	3.15 (0.69–14.5)	3.31 (0.65–16.9)
≤160	58/66 (87.9)	6/66 (9.1)	2/66 (3.0)	Reference	Reference
>105	20/26 (76.9)	4/26 (15.4)	2/26 (7.7)	3.58 (0.64–19.9)	3.78 (0.65–22.0)
>75.4–105	22/25 (88.0)	2/25 (8.0)	1/25 (4.0)	1.62 (0.25–10.7)	1.61 (0.24–10.7)
≤75.4	23/25 (92.0)	2/25 (8.0)		Reference	Reference

[a]Bold denotes confidence intervals which exclude the null value. NCTLD, National Center for Tuberculosis and Lung Diseases; MDR-TB, multidrug-resistant TB; TB, tuberculosis; AE, adverse event; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval; C_{min}, trough serum concentration; AUC_{0-24}, area under curve.
[b]Adjusted for age and gender.

were common, occurring in 40% of patients at an incidence rate of 46 per 100 person-years. However, these AEs were not treatment limiting, as no patients required linezolid interruption or dose reduction due to cytopenias, and most occurred several months into therapy. These findings suggest that long-term use of the 600-mg/day regimen, now standard due to toxicities associated with the 1,200-mg/day regimen, is well tolerated and safe for clinical use. Our findings contrast with those from other TB treatment cohorts using 1,200 mg/day, such as the Nix-TB trial in which most patients (93/109, 85%) required linezolid interruption or dose reduction during a 26-week course due to an AE (5). In a clinical trial using linezolid 600 mg/day, 18% of patients experienced a grade 3 or higher cytopenia AE, while most cytopenia AEs in our study were low grade and unlikely to be clinically significant (21). Additionally, almost all patients with cytopenias experienced count recovery within 2 months. The apparent tolerability of the 600-mg/day dose is consistent with PK modeling data that suggest this dose may minimize toxicity while maintaining efficacy (19, 22). Thus, our study

TABLE 5 Ordinal logistic regression analysis of linezolid exposure and degree of anemia among patients with MDR-TB ($n = 76$)[a]

Measure	No. of patients/total no. of patients (%) with AE grade of:			Data for higher-grade anemia (95% CI)	
	None	1	2–3	cOR	aOR[b]
Linezolid C_{min} (mg/L)	53 (69.7)	14 (18.4)	9 (11.8)		
>2	3/7 (42.9)		4/7 (57.1)	**13.33 (2.30–77.2)**[c]	**19.2 (2.49–149)**[c]
≤2	50/69 (72.5)	14/69 (20.3)	5/69 (7.3)	Reference	Reference
>0.35	15/26 (57.7)	4/26 (15.4)	7/26 (26.9)	2.52 (0.79–8.04)	1.93 (0.57–6.50)
>0.12–0.35	20/25 (80.0)	3/25 (12.0)	2/25 (8.0)	0.74 (0.20–2.77)	0.81 (0.21–3.11)
≤0.12	18/25 (72.0)	7/25 (28.0)		Reference	Reference
Linezolid AUC_{0-24} (mg·h/L)					
>160	5/10 (50.0)		5/10 (50.0)	**12.0 (2.41–59.8)**[c]	**8.74 (1.58–48.3)**[c]
≤160	48/66 (72.7)	14/66 (21.2)	4/66 (6.1)	Reference	Reference
>105	14/26 (53.9)	5/26 (19.2)	7/26 (26.9)	2.85 (0.89–9.06)	2.37 (0.71–7.90)
>75.4–105	21/25 (84.0)	2/25 (8.0)	2/25 (8.0)	0.58 (0.15–2.29)	0.63 (0.16–2.54)
≤75.4	18/25 (72.0)	7/25 (28.0)		Reference	Reference

[a]Bold denotes confidence intervals which exclude the null value. NCTLD, National Center for Tuberculosis and Lung Diseases; MDR-TB, multidrug-resistant TB; TB, tuberculosis; AE, adverse event; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval; C_{min}, trough serum concentration; AUC_{0-24}, area under curve.
[b]Adjusted for age & gender.
[c]Polytomous logistic regression for grades 2 to 3 versus none.

provides much-needed clinical safety data to support use of linezolid at a dose of 600 mg/day for treatment of MDR-TB.

Regression modeling suggests that cytopenia AEs, particularly thrombocytopenia, are associated with linezolid C_{min} and AUC_{0-24} using several different cutoffs, and higher-grade cytopenias are associated with higher PK parameter values. Relatively few (7/76, 9.2%) patients in this cohort had C_{min} values above the literature-informed 2-mg/L mitochondrial toxicity threshold compared to at least half of patients receiving linezolid 600 mg or 300 mg daily in studies of drug-resistant TB in South Africa (15, 22). However, the proportion above the toxicity threshold in the South African cohorts was higher than in other studies, and in a separate study, investigators suggested a toxicity trough concentration threshold of 2.5 mg/L (15, 23). This could reflect known heterogeneity between linezolid PK study populations and emphasizes the need for further evaluation of the utility of PK monitoring for linezolid (24). Recent evidence suggests the CYP450 2J2 enzyme accounts for approximately 50% of linezolid hepatic metabolism (25). Differences in CYP2J2 expression or other factors influencing its function, such as diet, could be responsible for variability in linezolid exposures in different populations (26). Contrasting toxicity or AE findings in different populations may also reflect the distribution of mitochondrial rRNA polymorphisms possibly associated with linezolid mitochondrial toxicity (16). Populations in the Caucasus region have low mitochondrial genetic diversity, so including patients from other settings would strengthen or confirm the findings of studies based in Georgia and add to the understanding of PK parameters in global populations (27).

While pharmacokinetic parameters could potentially identify patients at risk of linezolid toxicity, PK analysis for therapeutic drug monitoring (TDM) is not readily available in all centers (28). Although strategies have been proposed to address barriers to implementation, TDM is not currently generalizable to settings where most patients with MDR-TB are treated (29). Alternative linezolid dosing strategies, such as an intensive phase of 1,200 mg daily followed by dosing modification or discontinuation, have been proposed, and preliminary results from the ZeNix trial suggest that a reduced dose or duration of linezolid remains effective while enhancing safety (15, 30, 31). A recent PK modeling study using Nix-TB data supports this conclusion (32). The apparent safety and efficacy of long-term use of linezolid 600 mg/day is reassuring for settings where TDM and frequent laboratory monitoring are challenging.

The evidence from use of linezolid for treatment of Gram-positive bacterial infections indicates cytopenias develop early in therapy, within a few weeks of initiation (10). Among patients with drug-resistant TB treated with linezolid-containing regimens, cytopenias may occur later in the treatment course. In the Nix-TB trial, 52/109 (48%) patients developed cytopenias, with the majority occurring in the first 2 months of therapy, though the proportion was not quantified in study results (5). A study in South Africa of 151 patients reported a 6-month cumulative incidence of anemia of 39%, with a median time to event of 11 weeks (2.75 months) (23). However, in our cohort, the median time to development of cytopenias was 4 months for anemia and 11 months for thrombocytopenia; while this could be due to low linezolid exposure, population differences, or study sampling schedule, pending clinical trial data or further studies with larger sample size may inform whether CBC monitoring can be less frequent while on linezolid. In addition, other oxazolidinones such as sutezolid may offer improved safety profiles for treatment of TB in the future (33).

Our study is subject to certain limitations. Limitations include the single-country cohort, which may limit generalizability to other settings. Few patients had thrombocytopenia at baseline, and missing CBC data remained despite supplemental data collection, which could result in missed cytopenia AE. However, the median number of CBC collections was 11 among those who completed treatment, suggesting that CBC collection was robust for those who remained in care during the study period. Regression modeling produced broad CIs, which often include the null, though the direction of association is generally consistent except in the model evaluating anemia and tertiles

of linezolid exposure. The PK data are from a single time point, which may limit the association of PK parameters with incident cytopenias late in therapy and bias the results toward the null. Additionally, PK data for other drugs are not included in this analysis, though the drugs included in treatment regimens for these patients are unlikely to influence the development of cytopenias either directly or via drug-drug interactions and should not impact study findings. Strengths of our study include its population size for investigation of clinical and PK data, well-controlled dosing histories prior to PK sampling, and length of follow-up. Participants received linezolid as long-term therapy for a median of 17.5 months in a programmatic setting; newer linezolid-containing regimens are much shorter at 6 or 9 months (34). These aspects support the use of linezolid for the durations recommended to treat MDR-TB.

In conclusion, among a cohort of patients treated for MDR-TB with regimens containing linezolid 600 mg daily, cytopenias occurred frequently and at a median of 4 months but were of minimal clinical impact, as they did not limit treatment with long-term use. Incident cytopenias may be associated with pharmacokinetic parameters such as C_{min} when evaluated early in therapy; this warrants investigation in other settings to inform the utility of TDM. Our findings add to the evidence that this essential anti-TB drug is safe for use in programmatic management of MDR-TB.

MATERIALS AND METHODS

Design and population. This was a secondary analysis of a National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID)-funded prospective observational cohort of patients with MDR-TB initiating treatment at the National Center for Tuberculosis and Lung Diseases (NCTLD) in Tbilisi, Georgia (20, 35). Eligible patients were those ≥16 years with sputum culture-confirmed TB and multidrug resistance who initiated therapy with bedaquiline, linezolid, clofazimine, and/or delamanid from December 2015 to May 2017. Treatment regimens were individualized based on drug susceptibility testing (DST) results following National TB Program (NTP) and WHO guidelines. Treatment regimens were determined by the NTP Drug Resistance Committee, which meets twice weekly. The standard linezolid dose was 600 mg given once daily, and the standard of care for treatment duration during the study period was 20 to 24 months. Guidelines for linezolid dose reduction included an AE increase in grade to grade 2, which was determined to be related to linezolid, and the decision whether to dose reduce or pause linezolid administration was made by the NCTLD DR-TB Committee. All treatment was administered through directly observed therapy (DOT) at the NCTLD during initial hospitalization. After discharge, DOT was administered 6 days per week at the NCTLD ambulatory department or at 1 of 4 other TB dispensaries in Tbilisi. Medical records and patient interviews were used to collect demographics, medical history, and clinical and laboratory data, including adverse events. Written informed consent was required, and ethics approvals were obtained from the institutional review boards of Emory University and the NCTLD.

Measurements. Laboratory evaluation included monthly sputum cultures until conversion, defined as 2 consecutive negative sputum cultures ≥28 days apart and at least through 12 months of treatment. Patients were asked to return approximately 6 months posttreatment for follow-up and to provide a sputum sample. Sputum samples underwent acid-fast bacilli (AFB) smear microscopy, and AFB sputum cultures were performed at the National Reference Laboratory using Löwenstein-Jensen–based solid medium and the Bactec mycobacterial growth indicator tube 960 broth culture system. Positive cultures were confirmed to be *M. tuberculosis* complex using the *M. tuberculosis*-related antigen test. Phenotypic first- and second-line DST was conducted as previously described, and the MTBDR*plus* assay was performed on positive culture isolates (36). Neuropathy was assessed only while patients were hospitalized and was not a focus of this study.

CBCs were collected monthly for 12 months and up to 3 later time points at 13, 18, and 20 to 24 months. For pharmacokinetic analyses, 5 to 6 blood samples were collected predose and at 2, 4 to 6, 8 to 10, 12, and 24 h postdose 4 to 6 weeks after treatment initiation. Patients were hospitalized and receiving drugs via DOT for at least 7 days prior to PK sampling. Drug concentrations were measured at the Infectious Diseases Pharmacokinetics Laboratory at the University of Florida (19). Noncompartmental analysis was conducted using Phoenix v7.0 (Certara, Princeton, NJ, USA). Minimum serum concentration (C_{min}) and maximum serum concentration (C_{max}) were determined based on the time course of drug concentrations (37). Area under the curve (AUC) was estimated using the linear trapezoidal linear interpolation method.

Primary outcome. Incident cytopenias were evaluated using the NIH Division of AIDS (DAIDS) adverse event (AE) grading scale, which assigns increasing severity of AE from 1 through 4 with decreasing CBC parameters (38). For platelets, a value of $<125 \times 10^3/\mu L$ is grade 1, $<100 \times 10^3/\mu L$ is grade 2, $<50 \times 10^3/\mu L$ is grade 3, and $<25 \times 10^3/\mu L$ is grade 4 (Table 2). For hemoglobin, a value <11.0 g/dL is grade 1, <10.0 g/dL is grade 2, <9.0 g/dL is grade 3, and <7.0 g/dL is grade 4. For white blood cells, a value of $<2.5 \times 10^3/mm^3$ is grade 1, $<2.0 \times 10^3/mm^3$ is grade 2, $<1.5 \times 10^3/mm^3$ is grade 3, and $<1.0 \times 10^3/mm^3$ is grade 4. An incident cytopenia was defined as either a new graded CBC parameter AE from a previous normal value or an increase in a CBC AE grade if a person had an abnormal baseline

CBC parameter. Patients were only counted once when reporting the number of adverse events, and the reported grade was the lowest value in an individual patient.

Primary exposure. Linezolid exposure as measured by PK parameters was evaluated using values reported in the literature or tertiles of exposure. Previous studies have proposed a toxicity threshold of C_{min} of >7 mg/L or AUC_{0-24} of >280 mg·h/L for thrombocytopenia and an efficacy threshold of C_{min} of >2 mg/L or AUC_{0-24} of >160 mg·h/L (14, 39). A C_{min} value of >2 mg/L has also been associated with mitochondrial toxicity. Mouse models of TB have demonstrated an association between hemoglobin and linezolid dose and C_{min}, but not AUC (40). Among the study population, the median C_{min} was 0.235 mg/L (interquartile range [IQR], 0.069 to 0.529), and the median AUC_{0-24} was 89.6 mg·h/L (IQR, 69.2 to 116.2). Collected covariates included the baseline characteristics of body mass index, diabetes status, tobacco use, hepatitis B virus infection, cavitary TB disease, and extensive drug resistance, as well as treatment characteristics such as the duration of linezolid therapy, duration of second-line drug therapy, and duration of initial hospitalization.

Statistical analysis. To describe the incidence of cytopenias with cumulative proportion and incidence rate, person-time was calculated as time to incident cytopenia or assumed to be the 12-month duration of monthly CBC collection. Logistic regression was used to evaluate the relationship between linezolid PK exposure and development of cytopenias. The outcomes were any cytopenia, anemia, or thrombocytopenia anemia as defined by the NIH/DAIDS AE grading table. Exposures were C_{min} and AUC_{0-24} cutoffs from the literature and generated from the receiver operating characteristic (ROC) curve. Ordinal logistic regression was used to describe the dose-response relationship between linezolid PK exposure and severity of cytopenia. The outcomes were grade of anemia or thrombocytopenia as defined by the NIH/DAIDS AE grading table. The three levels of the outcome were none, grade 1, and grade 2 to 3 combined. There were no grade 4 AEs. Exposures were C_{min} and AUC_{0-24} cutoffs from the literature and tertiles of exposure. The proportional odds assumption was assessed using the score test. The proportional odds assumption was not met for the models evaluating anemia AE that used linezolid PK thresholds gathered from the literature (C_{min} of 2 mg/L and AUC_{0-24} of 160 mg·h/L), likely because there were no grade 1 AE in these categories; polytomous logistic regression for grade 2 to 3 anemia versus no anemia was used for these models. Age and gender were included in adjusted models because of the variability in CBC parameters with these characteristics. In univariate analysis, female gender was associated with anemia AE (see Table S1 in the supplemental material), but other potential covariates were not. A second adjusted model, including alcohol use and hepatitis C virus infection, was evaluated because of the potential clinical effect of these factors on CBC parameters via myelosuppression or liver disease. There was no evidence of collinearity between covariates. Models were compared by the likelihood ratio test for nested models.

Data availability. Data used in this analysis is available via the Emory Dataverse (https://doi.org/10.15139/S3/WL3O44).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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