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Proposed Linezolid Dosing Strategies to Minimize Adverse Events for Treatment of Extensively Drug-Resistant Tuberculosis

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Background. We evaluated Nix-TB trial data (NCT02333799, N = 109) to provide dosing recommendations to potentially minimize linezolid toxicity in patients with extensively drug-resistant tuberculosis. .

Methods. A pharmacokinetic model and toxicodynamic models for peripheral neuropathy, hemoglobin, and platelets were developed. Simulations compared safety outcomes for daily linezolid of 1200 and 600 mg, with and without dose adjustments for toxicity. Severe neuropathy was based on symptom scores from the Brief Peripheral Neuropathy Screen. Severe anemia and thrombocytopenia were defined as ≥ grade 3 adverse events according to the NIAID Division of Microbiology and Infectious Disease Adult Toxicity table.

Results. Predicted concentration-time profiles were a major predictor in all toxicodynamic models. Simulations showed higher percentages of patients with severe neuropathy (median, 19%; 90% confidence interval [CI], 17%–22% vs 5%, 4%–7%) and severe anemia (15%, 12%–17% vs 1%, 0%–2%) between 1200 and 600 mg daily linezolid. No differences in severe thrombocytopenia were observed (median, <1% for both daily doses). Generally, neuropathy occurred after 3 to 6 months of treatment and, with protocol-specified management, reversed within 15 months after onset. Simulations indicated that a >10% decrease in hemoglobin level after 4 weeks of treatment would have maximum sensitivity (82%) and specificity (84%) for predicting severe anemia. Reducing the dose from 1200 to 600 mg triggered by this marker may prevent 60% (90% CI, 45%–72%) of severe anemia.

Conclusions. Simple neuropathy symptom and hemoglobin monitoring may guide linezolid dosing to avoid toxicities, but prospective testing is needed to confirm the benefit-to-risk ratio.

Keywords. adverse events; drug-resistant tuberculosis; linezolid; PK–PD modeling; tuberculosis therapeutics.

Treatment success in patients with extensively drug-resistant tuberculosis (XDR-TB) is low (38%), and new drugs and regimens are needed to improve cure rates [1]. Here, XDR-TB is defined as resistance to isoniazid and rifampin (multidrug-resistant tuberculosis [MDR-TB]), plus at least 1 fluoroquinolone and 1 of 3 injectable drugs (definition prior to the World Health Organization's update of January 2021 [2]). Linezolid, a potent antimicrobial agent, is being repurposed against DR-TB and has been found effective when added to failing regimens [3, 4]. It was prioritized in 2018 for use against MDR-TB [5].

The phase 3 Nix-TB trial (NCT02333799) evaluated combination therapy with bedaquiline (400 mg once daily for 2 weeks, then 200 mg 3 times per week), pretomanid (200 mg once daily) and high-dose linezolid (starting dose of 1200 mg daily) (BPaL) for 6 months (option to extend to 9 months) against XDR-TB and treatment-intolerant or nonresponsive (TI/NR) MDR-TB. Patients with ≥ grade 3 peripheral neuropathy or ≥ grade 2 anemia or thrombocytopenia at pretreatment were excluded. Ninety-eight of 109 participants (90%) had negative mycobacterial cultures at 6 months after completion of treatment [6].

The US Food and Drug Administration and the European Medicines Agency approved BPaL for XDR-TB and TI/NR MDR-TB [6-9]. However, the dose of linezolid is controversial because of safety concerns. Linezolid binds to bacterial ribosomes that inhibit bacterial protein synthesis. Because bacterial ribosomes resemble mitochondrial ribosomes, linezolid also appears to inhibit mitochondrial protein synthesis, leading to mitochondrial toxicity-related adverse events, including myelosuppression and peripheral neuropathy [10]. In Nix-TB, adverse events (≥ grade 1) including peripheral neuropathy (81% of participants), anemia (37%), and thrombocytopenia (6%) led to linezolid discontinuations (28% of participants), interruptions (46%), and dose reductions (39%).

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Nonetheless, linezolid is among the most effective drugs for MDR-TB and XDR-TB [3, 6, 11]. Although linezolid trough levels >2 mg/L have been associated with linezolid-related adverse events in patients with XDR-TB, many patients (42%) with trough levels ≤2 mg/L still develop adverse events [12]. Moreover, trough levels are difficult to collect and measure in practice. Information is limited about optimal dosages, treatment durations, and best practices for linezolid in TB to maintain efficacy while minimizing adverse events. Here, using data from Nix-TB, we evaluated relationships between linezolid dosing, plasma concentrations, and time course of major toxicities. We provide practical, data-driven recommendations about linezolid dosing.

METHODS

Study Design

This study was based on data from Nix-TB [6]. Per discretion of the Nix-TB investigator, the linezolid dose could be reduced, interrupted, or discontinued after the first month of therapy for suspected linezolid-related toxicities. All dosage adjustments were recorded and used in our analysis. Participants in Nix-TB provided predose pharmacokinetic (PK) samples (trough levels) after treatment for 2, 8, and 16 weeks and, for a subset of participants, PK profiles after 16 weeks (Figure 1). Using the Brief Neuropathy Screen, peripheral neuropathy symptoms were assessed before, during, and up to 24 months after treatment. Blood counts were scheduled before and during treatment. Details on study design and data collection are available in Figure 1 and the Supplementary Methods.

Model Development

Model development began in April 2018 with data that became available in January 2018 and model testing was performed with data that became available in October 2020. Previously described PK models were tested to fit the PK data, including 1- and 2-compartment distribution models with linear and/or nonlinear kinetics [13-19] (Supplementary Tables 1 and 2; Supplementary Figure 1).

Assessments from the Brief Neuropathy Screen were categorized according to the maximum of 4 symptom scores as maximum score = 0, normal; 1–3, minimal; 4–7, modest; and 8–10, severe neuropathy. Proportions of participants in these categories over time were modeled by proportional odds (Supplementary Methods, Supplementary Table 3, Supplementary Figure 2).

For hemoglobin levels and platelet counts, linezolid's concentration effect was modeled as inhibiting the proliferation of progenitor cells or, more empirically, the synthesis of response in delayed-response PK–pharmacodynamic (PD) models (Supplementary Methods, Supplementary Tables 4–7, Supplementary Figure 1). An empirical model for rising hemoglobin levels in some participants (also seen in other data sources [20, 21]) was adjoined to the PK–PD model (Supplementary Methods, Supplementary Tables 4 and 5, Supplementary Figure 1). Similarly, normalization under treatment of elevated platelet counts in TB patients [21] was incorporated into our model (Supplementary Tables 6 and 7).

Model-based Simulations

The final models were used to perform simulations for 6 months after treatment initiation for myelosuppression and 24 months for neuropathy. Simulations assessed steady-state PK parameters

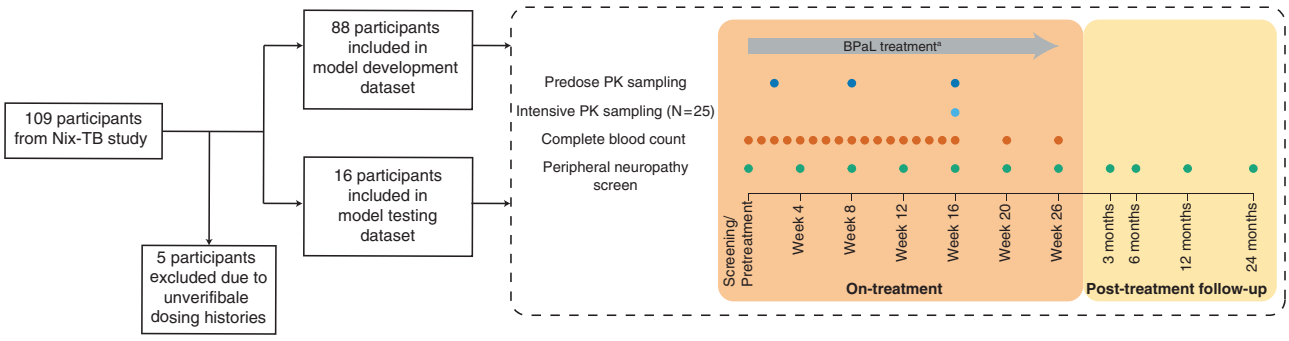

Figure 1. Nix-TB dataset and trial design diagram. Data from participants in Nix-TB with pulmonary extensively drug-resistant tuberculosis (TB) or treatment-intolerant or nonresponsive multidrug-resistant TB treated for 6 months (option to extend to 9 months) were used in this study. All participants were planned to provide predosing PK samples (trough levels) after treatment for 2, 8, and 16 weeks. In a subset of 25 participants, intensive PK sampling was planned at week 16 with samples collected at predose, 0.5, 1, 2, 4, 8, 12, 12.5, 13, 14, 16, 20, and 24 hours after dosing. Complete blood counts were scheduled at screening (up to 9 days prior to treatment initiation), at pretreatment (day 1 prior to dosing), weekly up to 16 weeks of treatment, and at 20 and 26 weeks of treatment. Brief Peripheral Neuropathy Screen was scheduled at screening; weeks 4, 8, 12, 16, 20, and 26 during treatment; and months 3, 6, 12, and 24 post-treatment. Diagram not drawn to scale. [a]Two participants had their treatment extended to 9 months. Additional complete blood counts and peripheral neuropathy screening were scheduled at weeks 30, 34, and 39 for these 2 participants (not shown in diagram). Abbreviations: BPaL, bedaquiline, pretomanid, and linezolid; PK, pharmacokinetic.

(area under the concentration-time curve over 24 hours, AUC; maximum concentrations, C_{max}; and minimum concentrations, C_{min}) evaluated 2 weeks after treatment initiation or dose adjustment; percentage of ≥ grade 3 myelosuppression according to the Division of Microbiology and Infectious Disease (DMID) Adult Toxicity table (severe anemia, hemoglobin level <8 g/dL; severe thrombocytopenia, platelet count $<50 \times 10^9$/L) [22]; percentages of neuropathy scores; and management and reversibility of toxicities (Supplementary Methods). We considered linezolid dosages of 600 or 1200 mg total daily (twice- or once-daily) for 6 months. Linezolid dosage reductions to 600 or 300 mg daily or discontinuations to manage toxicities were evaluated.

Although efficacy outcomes are not evaluated here, 2 PK-based efficacy metrics were assessed via simulations, based on the minimum concentration of linezolid at which 90% of clinical isolates are inhibited (MIC_{90}): (1) percentage of patients with ratio of free area under the concentration-time curve to MIC_{90} ($fAUC/MIC_{90}$) >119 and (2) percentage of time free concentrations are above MIC_{90} ($\%fT > MIC_{90}$) [19, 23-25]. The most commonly reported in vitro MIC_{90} of 0.5 mg/L against *Mycobacterium tuberculosis* was used [24, 26-29].

Statistical Analyses

Two approaches were used to evaluate associations of adverse events with linezolid exposure and other covariates. First, PK-toxicodynamic models (described above) were simulated to assess relationships between linezolid concentrations and toxicities. In this study, the terms "severe anemia" and "severe thrombocytopenia" are reserved to describe events defined using the PK-toxicodynamic models and DMID table (described above). Alternatively, investigator-reported adverse events, defined as ≥ grade 1 adverse events that were reported in Nix-TB, were also evaluated. Cox regression analysis was performed to identify predictors of investigator-reported peripheral neuropathy, anemia, and thrombocytopenia (Supplementary Methods). The area under the receiver operating characteristic curve (AUROC) was determined to assess model discrimination.

RESULTS

Eighty-eight of 109 participants (81%) were included in model development, 16 participants (15%) were used to test the models, and 5 participants (5%) were excluded because of unverifiable dosing histories. Participants who had different initial linezolid dosages (600 mg twice daily or 1200 mg once daily) had similar characteristics and pretreatment safety variables ($P > .05$; Table 1). From pretreatment to end of treatment, hemoglobin level increased (median, 12.1 vs 13.5 g/dL, $P < .001$), while platelet count decreased (median, 354 vs 262×10^9/L, $P < .001$). An interaction between initial dosage and time was observed for peripheral neuropathy scores ($P < .001$, generalized estimating equations [30]), suggesting higher scores in the twice-daily vs once-daily group during treatment. This interaction did not exist for hemoglobin levels or platelet counts (Figure 2B–D, left).

Investigator-reported peripheral neuropathy, anemia, and thrombocytopenia adverse events (≥ grade 1) were reported in 80 (77%), 38 (37%), and 6 (6%) of 104 participants, respectively. Investigator-reported hematologic adverse events occurred earlier (median, 8 weeks; 90% confidence interval [CI], 7–9) than neurological adverse events (14 weeks; 13–15). No relationship between investigator-reported peripheral neuropathy and anemia was observed ($P = .1$; Supplementary Table 8).

The frequency of severe neuropathy (scores, 8–10) peaked 3 to 6 months after beginning treatment (56 of 84, 67%, of severe neuropathy scores during this period) and declined by 24 months post-treatment (Figure 3). Three participants (3%) had severe neuropathy at 12 months post-treatment that was no longer severe 12 months later (Supplementary Figures 3 and 4). Four participants (4%) who did not have severe neuropathy at 12 months post-treatment had severe neuropathy 12 months later (Supplementary Figures 3 and 5).

The PK model included 2-compartment disposition with Michaelis-Menten elimination (Supplementary Table 1). Predicted individual concentration-time profiles that accounted for dosing histories better predicted neuropathy scores, hemoglobin levels, and platelet counts than observed trough levels in the PK-toxicodynamic models (Table 2). The exposure–response relationships were not affected by patients' age, sex, body weight, body mass index, or human immunodeficiency virus (HIV) status. Each model described its respective data reasonably well (Figure 2).

Simulated PK metrics of exposure are summarized in Table 3. At least 99% of patients simulated with 1200 mg total daily satisfied $fAUC/MIC_{90}$ >119, but only 64% with 600 mg once-daily and 56% with 300 mg twice-daily dosing (Table 3). Simulated toxicity profiles were similar between once- and twice-daily dosing at the same total daily doses (Table 3, Figure 4). However, simulations showed that more patients with severe neuropathy (median, 19%; 90% CI, 17–22) vs 5% (4–7) and severe anemia (15%, 12–17 vs 1%, 0–2) between 1200 and 600 mg daily linezolid. No differences in severe thrombocytopenia were observed (median, <1% for all doses tested).

Observed data and simulations showed that modest to severe neuropathy reversed to minimal or normal scores in most participants (78% in observed data; 92%–98% in simulated data) within 15 months after onset (Figure 5). Simulations showed linezolid discontinuation did not provide a substantial advantage over dosage reductions. For example, with an initial dosage of 1200 mg once daily, 95%, 95%, and 92% of simulated patients reversed neuropathy within 15 months after linezolid was

Table 1. Patient Characteristics and Summary of Data Available for Linezolid Model Development and Model Testing

Characteristic	Model Development		Model Testing
Initial Linezolid Dosage	600 mg Twice Daily	1200 mg Once Daily	1200 mg Once Daily
Participant characteristics, N/N (%)/median (minimum–maximum)			
Total number of participants	42	46	16
Men	23 (55)	23 (50)	7 (43)
Age, years	31 (18–55)	36 (21–60)	36 (17–48)
Body weight, kg	59 (29–112)	54 (33–89)	54 (32–106)
Body mass index, kg/m^2	19.8 (12.4–41.1)	19.7 (13.6–36.1)	18.9 (15.1–38.9)
Living with human immunodeficiency virus	18 (42)	25 (54)	7 (43)
Creatinine clearance, mL/min[a]	102 (46–167)	104 (42–180)	107 (43–179)
Pharmacokinetic,[b] N/N (%)			
Number of participants in intensive sampling substudy[b]	16 (38)	4 (8)	5 (31)
Total evaluable samples	243	154	100
Hemoglobin samples, N/N (%)/median (minimum–maximum)			
Hb samples per participants	19 (5–24)	19 (10–24)	20 (17–24)
Total evaluable samples	773	835	319
Pretreatment Hb level, g/dL	12.4 (8.5–16.1)	11.8 (8.7–15.6)	12.1 (7.4–13.9)
End of treatment Hb level, g/dL	13.6 (9.8–19.4)	13.7 (9.5–17.0)	12.8 (11.2–16.8)
Platelet samples, N/N (%)/median (minimum–maximum)			
Platelet samples per participants	19 (5–24)	19 (9–24)	19 (16–24)
Total evaluable samples	761	816	315
Pretreatment platelet count, $\times 10^9$/L	354 (137–1045)	348 (188–1083)	436 (139–730)
End-of-treatment platelet count, $\times 10^9$/L	254 (116–840)	262 (175–478)	312 (167–409)
Peripheral neuropathy,[c] N/N (%)/median (minimum–maximum)			
Neuropathy scores per participants	10 (2–14)	8 (3–11)	10 (10–13)
Total evaluable neuropathy scores	418	382	170
Pretreatment neuropathy scores, number of participants[c]			
None	32 (76)	31 (67)	16 (100)
Minimal	5 (12)	5 (11)	0 (0)
Modest	4 (10)	10 (22)	0 (0)
Severe	1 (2)	0 (0)	0 (0)
End-of-treatment neuropathy scores, number of participants[c]			
Normal	10 (24)	16 (35)	6 (38)
Minimal	9 (22)	8 (17)	3 (19)
Modest	8 (19)	12 (26)	7 (44)
Severe	10 (24)	7 (15)	0 (0)
Missing	5 (12)	3 (7)	0 (0)

N = 88 participants (model development) and 16 participants (model testing).

Abbreviation: Hb, hemoglobin.

[a]Calculated with the Cockcroft-Gault equation using serum creatinine levels and ideal body weight.

[b]All participants provided predosing pharmacokinetic (PK) samples (trough levels) after treatment for 2, 8, and 16 weeks, and a subset of 25 participants provided intensive PK samples after treatment for 16 weeks, with samples collected at predose and 0.5, 1, 2, 4, 8, 12, 12.5, 13, 14, 16, 20, and 24 hours after dosing.

[c]Levels based on maximum of 4 participant-elicited symptom question.

discontinued or reduced to 600 mg or 300 mg once daily, respectively (Figure 5B–D).

Based on observed data, hemoglobin level after 4 weeks of linezolid treatment had higher AUROC for predicting investigator-reported anemia adverse events (median, 0.71–0.73), which occurred at a median of 8 weeks (90% CI, 7–9) after treatment initiation, than hemoglobin level at earlier time points (0.50–0.63), observed linezolid trough levels (0.52), or participant characteristics (0.50–0.58; Figure 6A; Supplementary Table 11).

Similarly, in simulations with the hemoglobin model, the median time to onset of severe anemia was 10 weeks (90% CI, 9–11) and the AUROC was higher for hemoglobin level at 4 weeks than linezolid trough levels to predict severe anemia (.88, 90% CI, .85–.91, vs .64, .60–.69; Figure 6B). The threshold of 10% decrease in hemoglobin level at 4 weeks vs pretreatment had the highest sensitivity and specificity in predicting subsequent severe anemia (both >0.80). With this threshold as a trigger for dose reduction from 1200 to 600 mg once daily, simulations showed that the frequency of severe anemia events could potentially be decreased by a median of 60% (90% CI, 45–72), from 15% (12–17) to 6% (4–8; Table 3, Figure 7). When the threshold is met and dose is reduced, the median recovery is predicted to be 12 weeks (90% CI, 11–14) to pretreatment

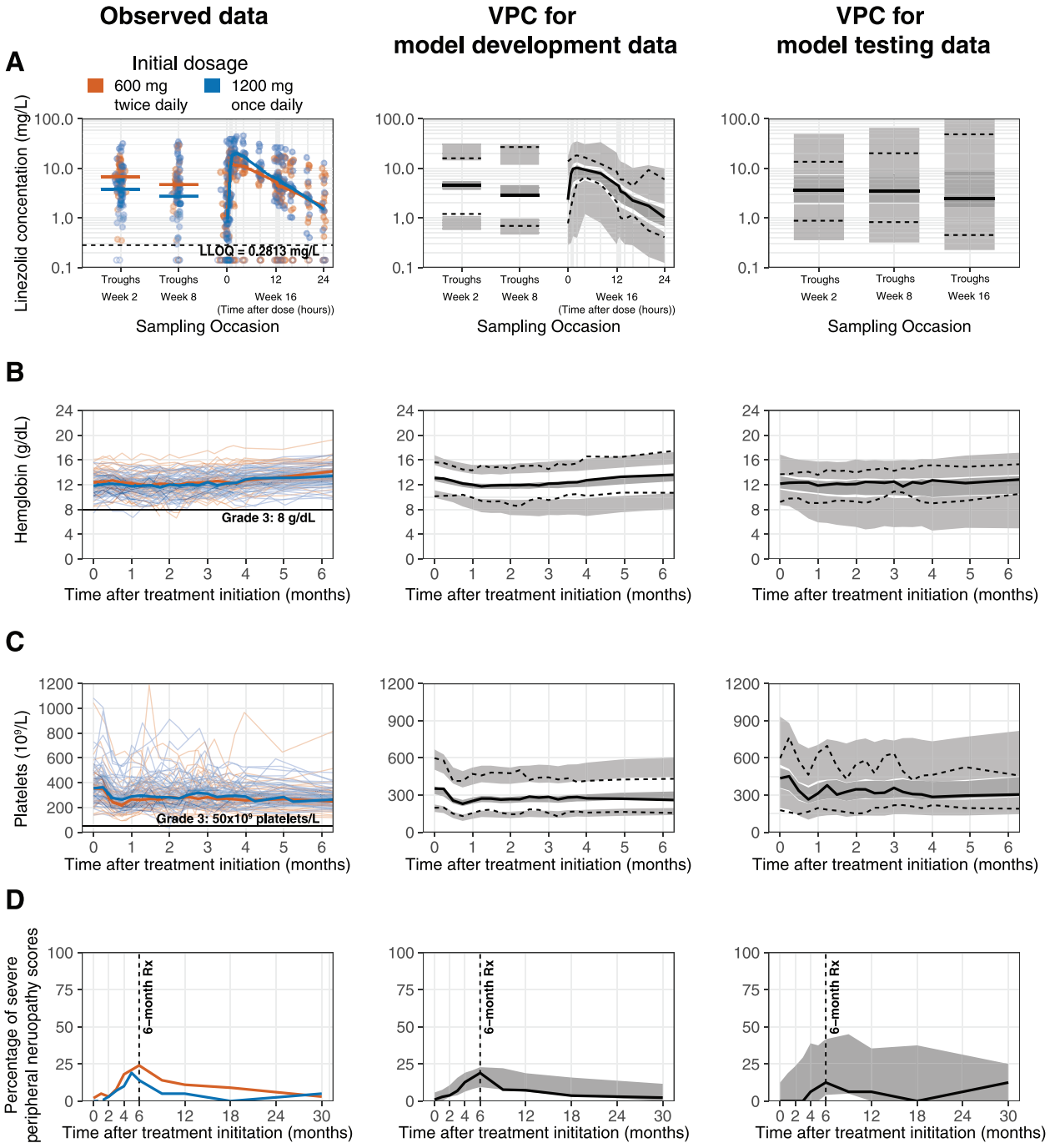

Figure 2. Linezolid pharmacokinetic-toxicodynamic models: observed data and visual predictive checks. *A,* Pharmacokinetic model for linezolid. Initial linezolid dosage: red, 600 mg twice daily; blue, 1200 mg once daily. *B,* Pharmacokinetic-toxicodynamic model for hemoglobin levels. *C,* Pharmacokinetic-toxicodynamic model for platelet counts. *D,* Pharmacokinetic-toxicodynamic model for severe peripheral neuropathy scores. Left, observed data. *A,* Observed linezolid concentrations (points) and median (thick solid line) stratified by initial linezolid dosage and sampling occasion. *B* and *C,* Observed hemoglobin levels and platelet counts (thin solid lines) and median (thick solid line) stratified by initial linezolid dosage. *D,* Observed percentage of severe peripheral neuropathy scores (thick solid line) stratified by initial linezolid dosage. Middle, VPC for model development data; right, VPC for model testing data. *A, B,* and *C,* Median (solid line) and 5th and 95th percentiles (dashed lines) of observed data, and 95% confidence intervals of the median and 5th and 95th percentiles of model predicted simulations (shaded areas). VPCs are prediction-corrected. The model testing data only included 5 patients with intensive pharmacokinetic (PK) sampling at week 16, so confidence intervals of the median and 5th and 95th percentiles substantially overlapped. Therefore, only linezolid trough levels are shown (collected from all patients) in the right column of *(A),* rather than the full 24-hour profile. *D,* Observed percentage of severe peripheral neuropathy scores (solid line) and 95% prediction interval of model predicted simulations (shaded area). Additional predictive checks for the PK model and peripheral neuropathy model available in Supplementary Table 9 and Supplementary Figures 6–8. Abbreviations: LLOQ, lower limit of quantification; Rx, treatment; VPC, visual predictive checks

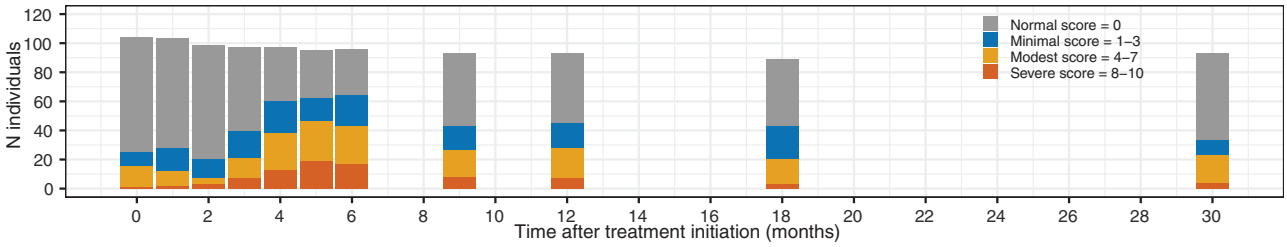

Figure 3. Distribution of peripheral neuropathy scores in Nix-TB. Distribution of peripheral neuropathy scores vs time in 104 participants (model development, 88 participants; model testing, 16 participants).

hemoglobin level and 7 weeks (6–8) to normal level (≥10.6 g/dL). Decreasing the linezolid dosage from 1200 to 600 mg in some patients for anemia did not substantially affect the overall rates of peripheral neuropathy (19% of patients with severe neuropathy when all patients administer 1200 mg once daily for 6 months vs 16% of patients after toxicity management strategy) or efficacy target attainment (100% of patients with fAUC/MIC >119 vs 89% of patients; Table 3). Dose adjustments to 300 mg once daily or discontinuation yielded similar results (data not shown).

DISCUSSION

In this study, we identified simple dosing strategies that may be considered for follow-up research on reducing linezolid toxicity. Model simulations showed that, as part of the 6-month BPaL regimen in patients with XDR-TB and TI/NR MDR-TB, frequencies of toxicity were comparable between once- and twice-daily dosing of linezolid at the same total daily dose but higher with higher total daily doses. Peripheral neuropathy typically improved after linezolid dosage reduction and should be monitored closely throughout treatment. Additionally, hemoglobin levels before treatment and after 4 weeks of treatment are hypothesized to guide early dosage adjustments to prevent severe anemia. Management strategies for severe thrombocytopenia were not investigated because it was infrequent (1 of 104 study participants). This work could be useful in designing future clinical trials to confirm the utility of the recommended strategies for improving patient safety while simultaneously assessing their impact on efficacy and, consequently, the benefit-to-risk ratio.

Peripheral neuropathy is the most frequent linezolid-related adverse event [6, 11, 31]. In Nix-TB, of 75 participants with modest or severe neuropathy scores, 71 had their first such score by 6 months and 46 had their first such score between 3 and 6 months, consistent with results elsewhere [32]. Peripheral neuropathy was typically reversible with linezolid dosage adjustments at the discretion of the Nix-TB investigators. Our simulations showed that linezolid discontinuation does not provide a substantial advantage over dosage reductions. Although these results are generally consistent with results from various studies, some have reported irreversible peripheral neuropathy [33, 34]. Therefore, close monitoring of peripheral neuropathy symptoms, at least monthly, is critical for early detection.

Severe anemia (≥ grade 3) emerged after 9 to 11 weeks of daily linezolid, consistent with results elsewhere [6, 11, 35]. Therefore, treatment changes for hemoglobin toxicity should begin within 2 months after initiation of linezolid therapy. Although linezolid concentration-time profiles affected toxicity, use of linezolid trough levels, as suggested elsewhere [12, 36], had low AUROC for predicting severe anemia (0.64; 90% CI, 0.60–0.69). Changes in hemoglobin level at 4 weeks vs pretreatment had higher AUROC (0.88; 0.85–0.91). The relation between linezolid concentration and hemoglobin level may be modulated by high interindividual variability in the exposure–response relationship (69% coefficient of variation for

Table 2. Change in Objective Function Value for Inclusion of Linezolid Drug Exposure as a Predictor of Linezolid-related Toxicities

	Investigator-Reported Adverse Events[a]			Toxicodynamic Modeling[b]		
Linezolid Exposure Variable	Peripheral Neuropathy	Anemia	Thrombocytopenia	Neuropathy Score	Hemoglobin Level	Platelet Count
Observed linezolid trough levels at 2 weeks	0	–2	–1	–1	–23	–190
	$P = .9$	$P = .2$	$P = .3$	$P = .9$	$P = .4$	$P << .001$
Linezolid concentration-time profiles	Not tested	Not tested	Not tested	–125[c]	–414	–588
				$P << .001$	$P << .001$	$P << .001$

[a]Change in objective value with *P* values for inclusion of covariates as predictors of time to investigator-reported adverse event (≥ grade 1) in Cox regression analysis. The reported *P* values account for degrees of freedom when including covariate in model.

[b]Change in objective value with *P* values for inclusion of covariates as predictors of longitudinal hemoglobin level, platelet count, and neuropathy score in the toxicodynamic models. The reported *P* values account for degrees of freedom when including covariate in model.

[c]Concentrations in effect compartment were used in this model. Full details in the Supplementary Methods.

Table 3. Simulated Pharmacokinetic, Efficacy, and Toxicity Parameters After Total Linezolid Daily Doses of 600 mg or 1200 mg and Proposed Dosage Adjustments for Management of Severe Anemia Toxicity

Parameter	600 mg Total Daily Dose for 6 Months		1200 mg Total Daily Dose for 6 Months		Initial 1200 mg Once Daily, Then Management Strategy for Severe Anemia 4 Weeks After Treatment Initiation (Figure 7A)[a]		
	300 mg Twice Daily	600 mg Once Daily	600 mg Twice Daily	1200 mg Once Daily	Patients for Whom Dosage Continues at 1200 mg Once Daily Unchanged	Patients Who Meet Trigger Criteria and Dosage Is Reduced to 600 mg Once Daily	All Patients[b]
Pharmacokinetics–pharmacodynamics (median [90% prediction interval] or median [90% confidence interval] for percentages)							
C_{max} (mg/L)	6 (3–10)	9 (5–16)	14 (8–33)	22 (11–42)	22 (12–41)	8 (5–15)	19 (7–39)
C_{min} (mg/L)	2.1 (0.5–5.7)	1.0 (0.2–4.1)	6.6 (1.4–24.0)	3.9 (0.6–19.9)	4.0 (0.6–21.1)	0.9 (0.2–3.5)	2.6 (0.3–19.5)
AUC (mg × h/L)	91 (51–180)	99 (55–189)	249 (120–671)	273 (138–695)	274 (148–721)	92 (52–177)	226 (73–630)
%fT > MIC_{90}[c]	100 (79–100)	100 (56–100)	100 (100–100)	100 (86–100)	100 (86–100)	100 (55–100)	100 (69–100)
Percent of patients with fAUC/MIC_{90} > 119[c]	56 (52–59)	64 (62–68)	99 (99–100)	100 (99–100)	100 (99–100)	59 (55–63)	89 (87–97)
Peripheral neuropathy (median [90% confidence interval])							
Percent of patients with normal scores at 6 months	66 (63–69)	64 (61–67)	37 (35–40)	35 (33–38)	35 (32–37)	56 (50–61)	41 (38–43)
Percent of patients with minimal scores at 6 months	15 (13–18)	16 (13–18)	18 (15–21)	18 (15–21)	18 (16–21)	17 (13–23)	18 (16–21)
Percent of patients with modest scores at 6 months	14 (12–16)	15 (12–17)	27 (24–30)	27 (24–31)	27 (24–31)	18 (13–24)	25 (22–28)
Percent of patients with severe scores at 6 months	5 (4–6)	5 (4–7)	18 (16–21)	19 (17–22)	19 (16–22)	8 (5–12)	16 (14–18)
Anemia (hemoglobin level toxicity model) (median [90% confidence interval])							
Percent of patients with grade 3 or greater toxicity (hemoglobin <8 g/dL)	< 1 (0–2)	1 (0–2)	19 (16–22)	15 (12–17)	5 (4–7)	9 (7–11)	6 (4–8)
Percent of patients with early dose reduction	5 (3–6)	5 (3–6)	27 (23–30)	25 (22–29)	0	100	25 (22–29)
Thrombocytopenia (platelet count toxicity model) (median [90% confidence interval])							
Percent of grade 3 or greater toxicity (platelets < 50 × 10^9/L)	< 1 (0–<1)	< 1 (0–<1)	< 1 (0–<1)	< 1 (0–<1)	< 1 (0–<1)	< 1 (0–<1)	< 1 (0–<1)

Abbreviations: %fT > MIC_{90}, percentage of 24-hour time period free concentrations are above MIC_{90} (range from 0% to 100%); AUC, area under the linezolid concentration-time curve over 24 hours; C_{max}, maximum linezolid concentration; C_{min}, minimum linezolid concentration; fAUC/MIC_{90}, ratio of the free AUC to MIC_{90}; MIC_{90}, minimum concentration of antibiotic at which 90% of the isolates are inhibited.

[a]The simulated toxicity management strategy starts with all patients on a linezolid dosage of 1200 mg once daily. Individual hemoglobin levels are monitored weekly, and a >10% decrease in hemoglobin at 4 weeks relative to pretreatment triggers a dosage reduction to 600 mg once daily. Patients who do not meet this trigger criteria continue at 1200 mg once daily unchanged.

[b]Parameters for entire simulated population that includes patients for whom linezolid dosage continues at 1200 mg once daily unchanged and patients who meet trigger criteria and dosage is reduced to 600 mg once daily.

[c]MIC_{90} of 0.5 mg/L was used for all calculations. This value is based on the most commonly reported linezolid in vitro MIC_{90} against susceptible and resistant *Mycobacterium tuberculosis* in previous studies [24, 26–29]. Supplementary Table 10 shows pharmacokinetic-based efficacy metrics when using the lower (0.125 mg/L) and upper (1 mg/L) range of reported MIC_{90} values.

half-maximal inhibitory concentration, $IC_{50_{Hb}}$; Supplementary Tables 4 and 5). Therefore, close monitoring of hemoglobin levels is likely needed for early identification of linezolid-related anemia, with weekly monitoring to at least 2 or 3 months after starting linezolid therapy when severe anemia is typically observed. The threshold of >10% decrease in hemoglobin level at 4 weeks vs pretreatment may optimize the sensitivity and specificity of the hemoglobin level in predicting anemia and may prevent 60% of occurrences of severe anemia, with a false-positive rate of only 14% of patients who would undergo unnecessary linezolid dosage adjustments from 1200 mg to 600 mg once daily.

Linezolid-related adverse events are thought to be associated with mitochondrial toxicity [10]. In a previous study,

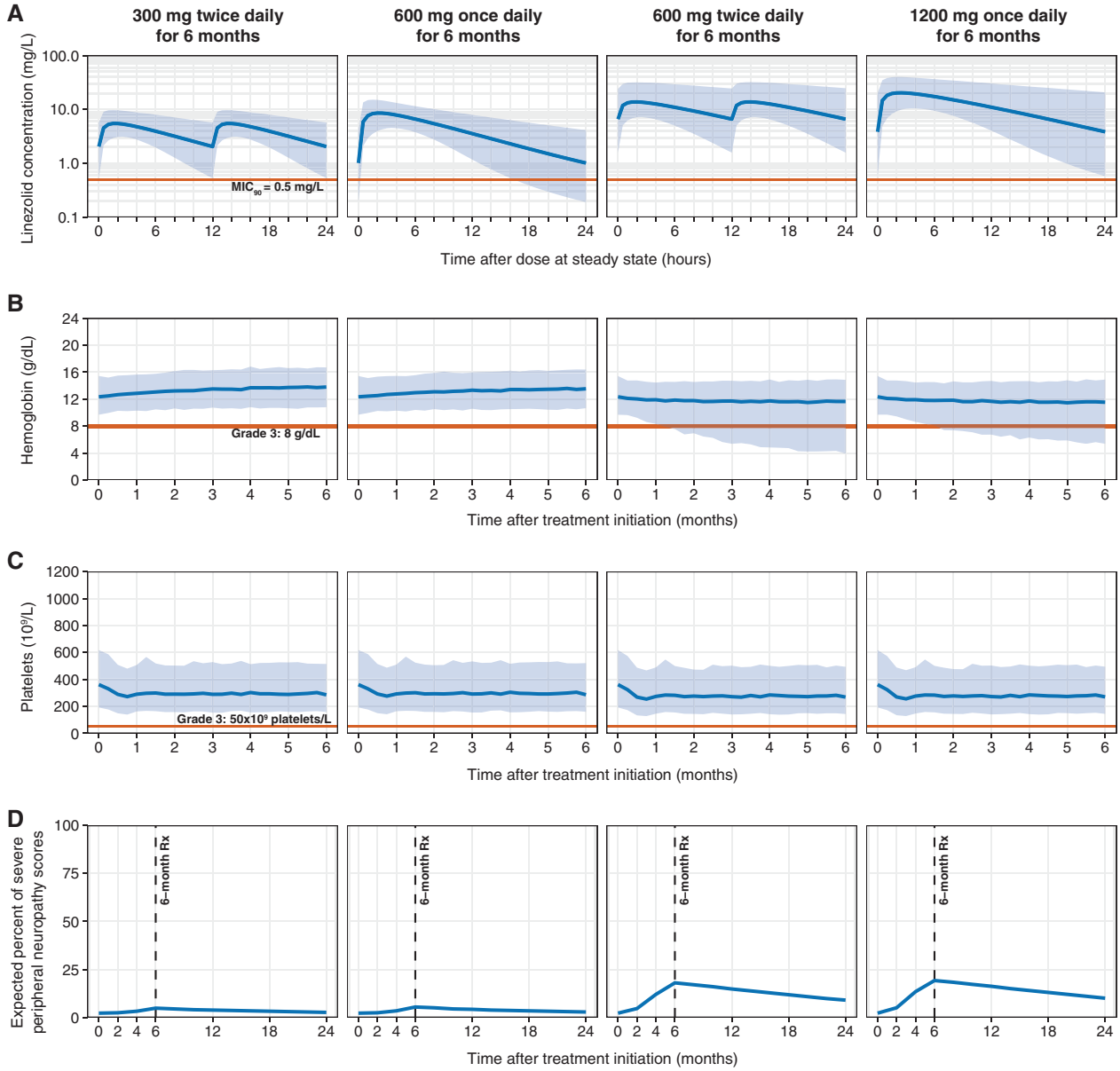

Figure 4. Simulated pharmacokinetic and toxicity profiles after total linezolid daily doses of 600 mg or 1200 mg. *A,* Simulated steady-state pharmacokinetic profiles evaluated 2 weeks after treatment initiation. Solid blue lines, typical participant (median of simulations); shaded areas, 90% prediction intervals; solid red line, MIC_{90} of 0.5 mg/L. *B,* Simulated hemoglobin level profiles for 6 months of treatment with linezolid. Solid blue lines, typical participant; shaded areas, 90% prediction intervals; solid red line, DMID definition of grade 3 toxicity (hemoglobin level <8 g/dL). *C,* Simulated platelet count profiles for 6 months of treatment with linezolid. Solid blue lines, typical participant; shaded areas, 90% prediction intervals; solid red line, DMID definition of grade 3 toxicity (platelet count $<50 \times 10^9$/L). *D,* Simulated expected percentages of severe peripheral neuropathy scores for 6 months of treatment with linezolid and 18 months of follow-up. Simulated percentages of normal, minimal, and modest score available in Supplementary Figure 9. First column, linezolid dosage 300 mg twice daily for 6 months; second column, linezolid dosage 600 mg once daily for 6 months; third column, linezolid dosage 600 mg twice daily for 6 months; fourth column, linezolid dosage 1200 mg twice daily for 6 months. Abbreviations: DMID, Division of Microbiology and Infectious Diseases; MIC_{90}, minimum concentration of antibiotic at which 90% of the isolates are inhibited.

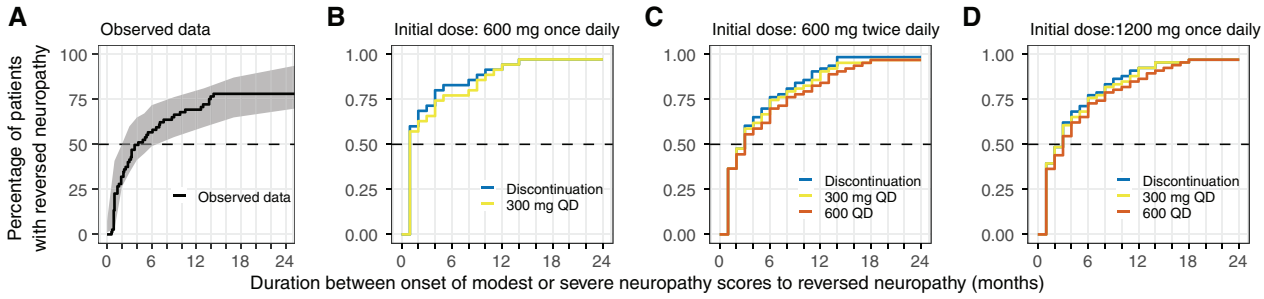

Figure 5. Reversibility of peripheral neuropathy associated with linezolid treatment. *A,* Percentage of participants with peripheral neuropathy reversed. Solid line, observed data; shaded area, 95% prediction interval from model simulations that account for actual dosage histories. *B, C,* and *D,* Percentage of participants with peripheral neuropathy reversed based on simulated data: *B,* Initial linezolid dosage 600 mg once daily. *C,* Initial linezolid dosage 600 mg twice daily. *D,* Initial linezolid dosage 1200 mg once daily. Neuropathy reversal was assessed by defining the first occurrence of a modest or severe neuropathy score as an event, and linezolid dosage was adjusted at the time of the event using simulations. After dosage adjustment, the time of reversal was defined as the time of the first of 2 consecutive minimal or normal scores. The distribution of time from the event to reversed neuropathy was plotted. Reduced dosage: red, 600 mg once daily; yellow, 300 mg once daily; blue, linezolid discontinued. The point at which each curve crosses the dashed black line is the time from dosage reduction to reversal of neuropathy in 50% of patients. Abbreviation: QD, once daily.

linezolid trough levels were associated with decreased mean mitochondrial function demonstrated by declining cytochrome c oxidase activity (measure of extent of mitochondrial protein synthesis) per unit citrate synthase activity (marker of mitochondrial mass) [12]. In that study, a clinically defined adverse event developed in all patients with trough level >2 mg/L but in less than half of patients with trough level ≤2 mg/L [12]. Generally, for bacterial infections, a higher threshold of trough levels >9 mg/L is accepted to be associated with increased risk of linezolid-related adverse events [14, 36-38]. However, 2 studies in patients with MDR-TB showed insignificant differences of linezolid trough levels (and AUC) between patients who experienced or did not experience adverse events [32, 34]. In our analysis, linezolid trough levels

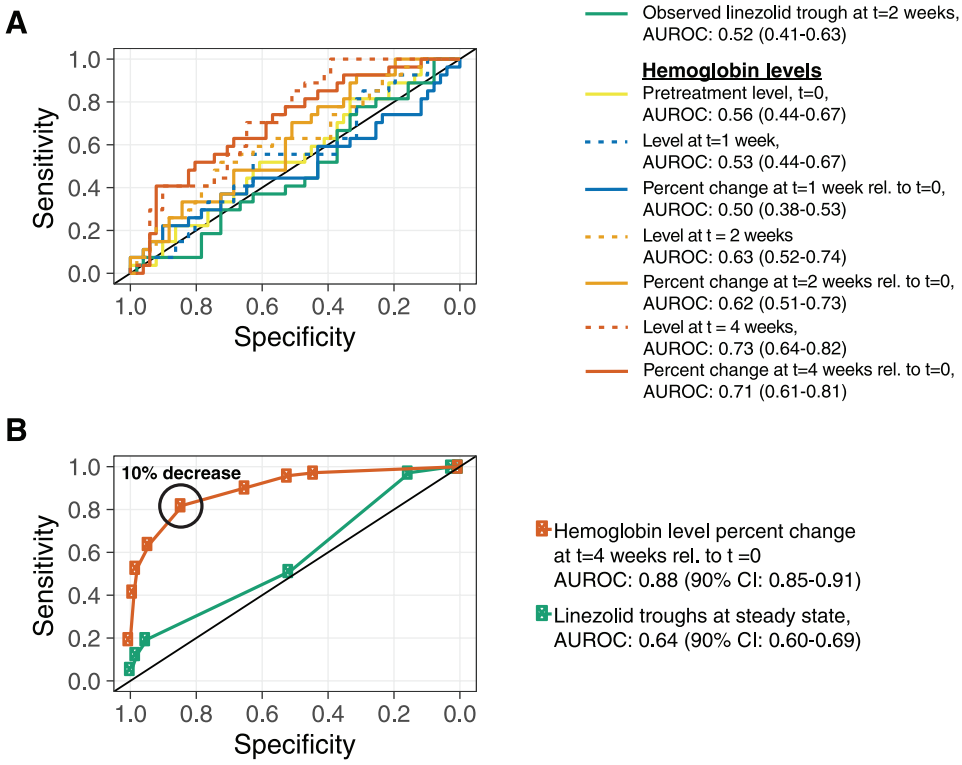

Figure 6. Predictors of anemia associated with linezolid treatment. *A,* Receiver operating characteristic curves for univariate models that predict investigator-reported anemia adverse events, defined in the Nix-TB trial. Additional models available in Supplementary Table 11. *B,* Receiver operating characteristic curves for simulated prediction of severe anemia using the hemoglobin level pharmacokinetic-toxicodynamic model, defined by Division of Microbiology and Infectious Diseases ≥ grade 3 toxicity (hemoglobin level <8 g/dL). Use of a 10% decrease in hemoglobin levels after 4 weeks of linezolid treatment to predict severe anemia maximizes sensitivity (0.82) and specificity (0.84; black circle). Abbreviations: AUROC, area under the receiver operating characteristic curve; t, time after treatment initiation; rel. to, relative to.

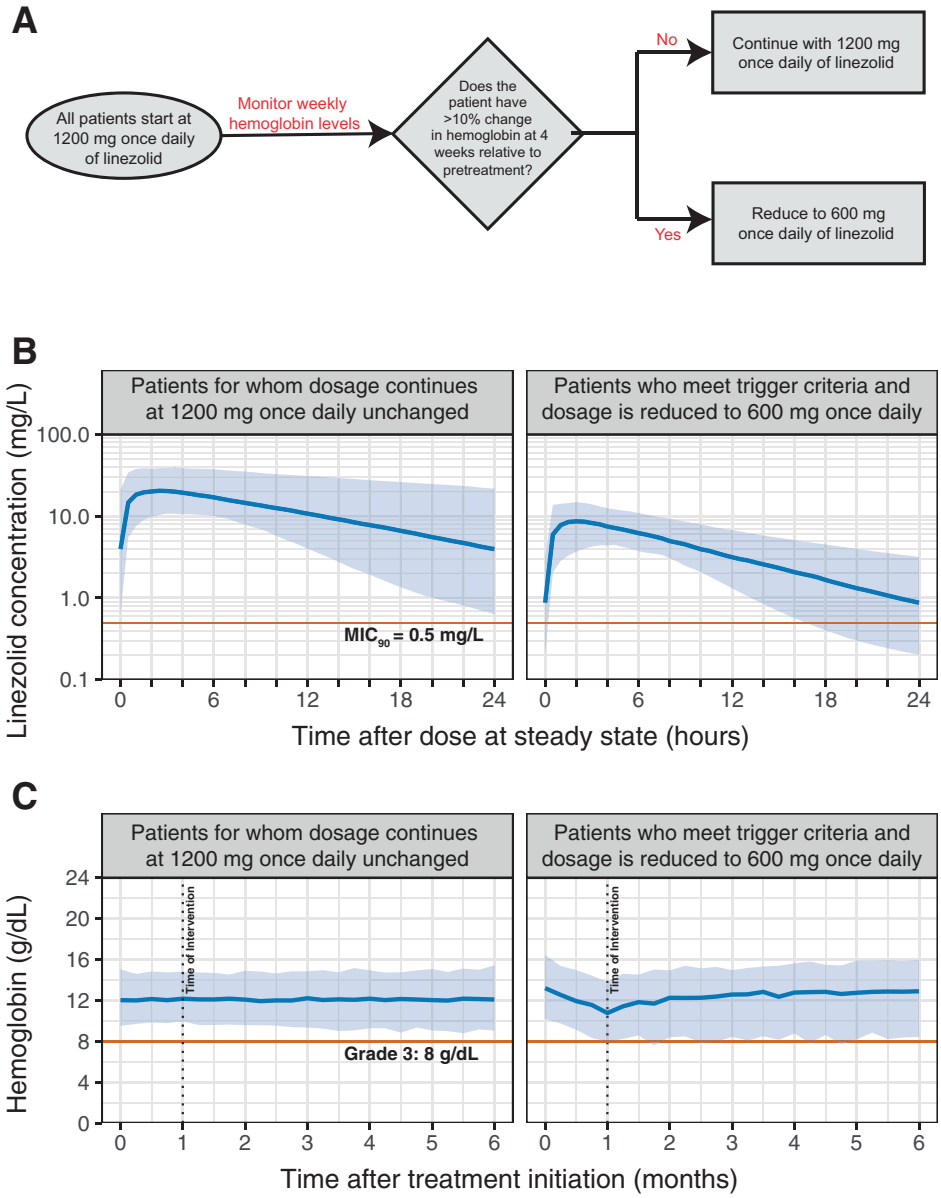

Figure 7. Proposed management strategy to predict and minimize severe anemia associated with linezolid treatment. *A,* Decision tree algorithm. *B,* Simulated steady-state pharmacokinetic profiles evaluated 2 weeks after implementing anemia toxicity management strategy (ie, 6 weeks after treatment initiation) for initial linezolid dosage 1200 mg once daily. Solid blue lines, typical participant (median of simulations); shaded areas, 90% prediction interval; solid red line, MIC_{90} of 0.5 mg/L. *C,* Simulated hemoglobin level profiles after implementing anemia toxicity management strategy for initial linezolid dosage 1200 mg once daily. Solid blue lines, typical participant (median of simulations); shaded areas, 90% prediction interval; solid red line, Division of Microbiology and Infectious Diseases definition of grade 3 toxicity (hemoglobin level <8 g/dL); black dashed line, intervention timepoint (4 weeks after treatment initiation) where decision is made for toxicity management strategy. Abbreviation: MIC_{90}, minimum concentration of antibiotic at which 90% of the isolates are inhibited.

predicted toxicity to platelets but not hemoglobin or neuropathy. Indeed, use of more informative concentration-time profiles that account for dosage adjustments better predicted all 3 toxicities at the individual level (Table 2). Regardless, we found that monitoring simple toxicity markers throughout treatment accurately informed and predicted toxicities, which is more practical than therapeutic drug monitoring in clinical settings. However, linezolid trough levels may still be valuable for the assessment of toxicity at the population level (eg, BPaL in a different population or linezolid as part of a different regimen) and should be collected, if possible, and compared with data from this study, among others.

Our simulations showed that linezolid at lower dosages reduced the occurrence of adverse events, but PK-based efficacy metrics (eg, fAUC/ MIC_{90} >119) suggest treatment efficacy may be compromised (Table 3). However, a clear link between PK-based metrics and clinical outcomes has yet to be established. The ZeNix trial (NCT03086486), a successor of

Nix-TB, that evaluated varied linezolid starting daily doses and durations may provide more reliable evidence on clinical outcomes. Our model predicts the following rates of severe neuropathy and anemia for regimens tested in ZeNix: 42% and 15% in 1200 mg linezolid for 6 months, 22% and 8% in 1200 mg for 2 months, 18% and 1% in 600 mg for 6 months, and 12% and <1% in 600 mg for 2 months (Supplementary Table 12), consistent with recently presented results from ZeNix [39]. Our study will be further validated as ZeNix data become available.

Strengths of our study include the enrollment of participants from sites in South Africa, which has among the highest national TB burden globally and a high percentage (48%, 50 of 104) of participants with HIV coinfection [40]. Additionally, the data were voluminous, including 497 linezolid plasma concentrations, 1927 hemoglobin levels, 1892 platelet counts, and 970 neuropathy scores. Therefore, our models described the longitudinal changes in linezolid PK and linezolid-related toxicity that occur among patients treated for TB and enabled unique evidence-based recommendations about treatment to predict and minimize linezolid-related toxicity.

Limitations of our study include the evaluation of linezolid as a component of BPaL combination therapy in XDR-TB and TI/NR MDR at sites only in South Africa, which may limit generalizability to other therapies or TB populations. Second, we did not consider treatments for toxicities other than linezolid dosage reduction or discontinuation. Third, we did not model the effects of dose adjustments on efficacy, although this limitation may be mitigated, in part, by the results of our simulations that evaluated PK-based efficacy targets.

In conclusion, we provide simple, data-driven recommendations for linezolid dosage adjustments that use practical toxicity markers for decision-making. We recommend that patients who start with a 1200-mg total daily dose be evaluated at pretreatment and monitored at least monthly during treatment for peripheral neuropathy symptoms to enable early detection. Dose adjustments for peripheral neuropathy should be made at the discretion of the clinicians and researchers. Further, hemoglobin levels should be evaluated at pretreatment and monitored at least weekly after linezolid initiation. Dose reductions to 600 mg total daily should be made at 4 weeks for patients with >10% decrease in hemoglobin level relative to pretreatment level. In Nix-TB, severe thrombocytopenia was infrequent, so more data are required to derive recommendations. Last, although linezolid trough levels were inferior for predicting toxicity compared with simple toxicity markers, we still recommend that they be collected and used to further assess their ability to predict toxicity at the population level. Our recommendations may help clinicians and researchers predict and minimize toxicity from linezolid treatment for XDR-TB and TI/NR MDR TB. Nonetheless, prospective studies are needed to test the proposed dosing strategies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M. Z. I., J. R. N., and R. M. S. contributed to study conception, study design, and data verification. M. Z. I. performed the data analysis, modeling, and simulation and prepared figures and tables, with support from J. R. N. and R. M. S. The first draft was written by M. Z. I., J. R. N., and R. M. S., and M. Z. I., J. R. N., F. C., and R. M. S. discussed the results and implications, critically revised the article, and approved the final version for publication.

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