3968

CLINICAL PHARMACOKINETICS AND TOXICODYNAMICS OF LINEZOLID IN NIX-TB TRIAL

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BACKGROUND

The FDA recently approved pretomanid along with bedaquiline and a high dose of linezolid (1200 mg QD) for 6 months' treatment in extensively drug resistant (XDR) and treatment intolerant or non-responsive multidrug resistant tuberculosis (TI/NR MDR-TB) patients based on the efficacy and safety data gathered from the NiX-TB trial.

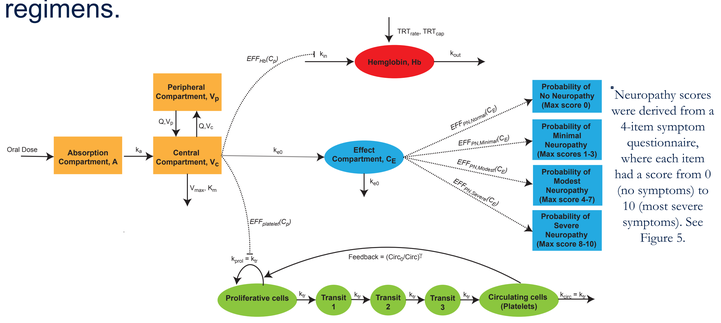
Limited high-quality data is available on pharmacokinetics (PK) and safety profiles following long-term use of high dose linezolid.

The current study used data collected from the NixTB trial to characterize the relationship between linezolid concentrations and toxicity (anemia, thrombocytopenia, and neuropathy) and to predict the time course and extent of toxicity for high-dose, long-term use of linezolid, as well as alternative dosing regimens to manage toxicities

METHODS

Population PK and PK-toxicodynamic models that account for individual dosing histories were developed.

Final models (Fig. 1) were used to simulate and compare PK and safety outcomes following various linezolid dosing regimens.



*Neuropathy scores were derived from a 4-item symptom questionnaire, where each item had a score from 0 (no symptoms) to 10 (most severe symptoms). See Figure 5.

Fig. 1 Final structural pharmacokinetic/toxicodynamic model.

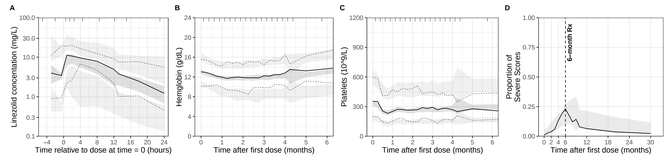


Fig. 2 Visual predictive checks for population (A) PK, (B) PK-hemoglobin, (C) PK-platelets and (D) PK-peripheral neuropathy models. Solid lines show observed median or proportion, dashed lines show 95% CI of observed data. Shaded areas show 95% CI or 95% PI.

Baseline and week 4 hemoglobin levels might be useful to guide early dose adjustments to prevent anemia (efficacy not considered). Most peripheral neuropathies reversed. NiX-TB patient management strategy effectively addressed safety.

RESULTS

- Of 109 enrolled patients, 104 with verifiable and complete dosing history were included in analysis.
- Linezolid PK was nonlinear. Simulations showed 0.37-fold decrease in steady state AUC when decreasing dose from 1200 to 600 mg QD (262 vs 97 mg/kg*h),
- Hematological toxicities and peripheral neuropathy were delayed and significantly related to dynamic linezolid PK (p< 0.001).
- Simulated median onset of anemia was 9 weeks with 16% of patients experiencing Grade 3 or greater toxicity for 1200 mg QD dose (Table 1). Consistent with anemia reported for ~40% of patients.
- PK-Platelet effect was small (Table 1). Consistent with thrombocytopenia only reported in 6% of patients.
- Severe cases of peripheral neuropathy peak at 6 months with 18% of patients experiencing severe scores and reduced to 2% at month 32 (Fig. 2D).

Table 1 Summary of simulated PK and toxicity parameters following linezolid at 1200 mg QD and proposed dose adjustments for management of anemia. Simulation performed for 500 patients.

	1200 QD for 6 months	1200 mg QD then 600 mg QD at week 4 for management of anemia
Pharmacokinetics - Pharmacodynamics		
CMAX (mg/L) [Median (95% PI)]	21 (10-51)	17 (5-46)*
CMIN (mg/L)	3.9 (0.8-15)	3 (0.5-12.9)*
AUC over 24 h (mg/L*h)	262 (138-561)	228 (68-564)*
Anemia		
% of patients with Grade 3 or greater toxicity (< 8 g/dL)	16	6
% of patients with early dose reduction	29	-
Platelets		
% of Grade 3 or greater toxicity (< 50x10^9 Platelets/L)	< 1	< 1
Peripheral Neuropathy		
% of patients with severe scores at 6 months	27	5

*Pharmacokinetic parameters at new steady state following proposed management strategy at week 4 for all patients, with or without dose adjustment.

RESULTS

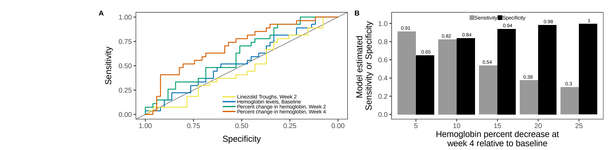


Fig. 3 Sensitivity and specificity rates for predicting (A) reported anemia events and (B) model simulated Grade 3 anemia.

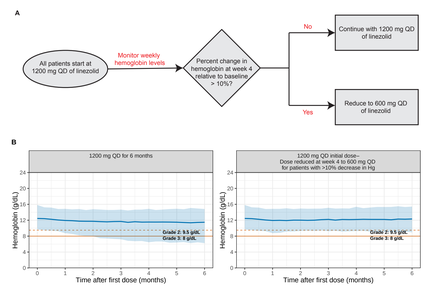


Fig. 4 (A) Proposed management strategy to prevent severe anemia cases. (B) Simulated hemoglobin profiles for 6-months of 1200 mg QD dose (left) and for 6-months of initial 1200 mg QD dose then implementation of anemia management strategy (right). Median and 90% prediction interval shown.

- Change in hemoglobin levels better predict reported anemia compared to linezolid troughs (Fig. 3A).
- Simulations suggest threshold of >10% decrease in hemoglobin levels at week 4 maximize sensitivity and specificity rates when predicting anemia (Fig. 3B).
- Simulations showed reducing daily dose from 1200 to 600 mg at week 4 for patients above threshold could potentially prevent 63% of anemia cases (16% to 6% cases, Table 1 and Fig. 4).

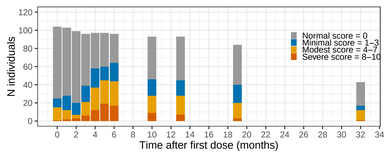
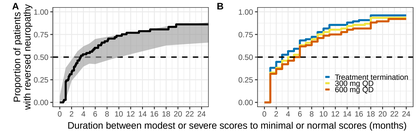


Fig. 5 (left) Distribution of maximum symptoms score from patient reported scores on i. interference with walking or sleeping, ii. pain, aching, or burning in feet or legs, iii. pins and needles in feet or legs, iv. numbness in feet or legs.

Fig. 6 (right) Proportion of patients with reversed neuropathy (A) in observed data [observed median and model simulated 90% PI] and (B) per model simulations of indicated dose adjustments.



- Some baseline peripheral neuropathy is prevalent (Fig. 5).
- Majority of patients who have completed two years post treatment follow-up reversed or are improving (Fig. 5).
- Observed data and simulations show majority of patients reverse from modest or severe scores to minimal or normal scores 2-6 months after dose adjustments (Fig. 6).