# Linezolid for Drug-Resistant Tuberculosis

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The development of a highly effective, oral, 6-month regimen for the treatment of multidrug-resistant tuberculosis, which previously took 18 to 24 months to cure, is one of the defining achievements of the tuberculosis research community in this century. The results of the Nix-TB study, which were published in the *Journal* in 2020,[1] showed that the combination of two new drugs, bedaquiline and pretomanid, with a repurposed oxazolidinone antibiotic agent, linezolid, given for 6 to 9 months to patients with drug-resistant or complicated multidrug-resistant tuberculosis, resulted in a favorable outcome in 98 of 109 patients (90%) at 6 months after the end of treatment. However, the efficacy of the regimen came at a cost — peripheral neuropathy developed in 88 patients (81%), and myelosuppression developed in 52 patients (48%). Both these conditions are well-recognized complications of prolonged linezolid treatment.

In this issue of the *Journal*, Conradie and colleagues[2] report on the ZeNix trial, which addresses the question of whether decreases in the duration of linezolid treatment given at the same dose (1200 mg daily) that was administered for 26 weeks in the Nix-TB study would result in a similar efficacy with a better side-effect profile. A total of 181 participants were enrolled; those from South Africa or the country of Georgia were 14 years of age or older, and those from Moldova or Russia were at least 18 years of age. All the participants had highly drug-resistant pulmonary tuberculosis, and 88% had extensively drug-resistant (XDR) tuberculosis (i.e., tuberculosis that was resistant to rifampin as well as to a fluoroquinolone and an injectable antituberculosis agent) or pre-XDR tuberculosis (i.e., tuberculosis that was resistant to rifampin as well as to either a fluoroquinolone or an injectable antituberculosis agent). The participants were randomly assigned to receive bedaquiline and pretomanid for 26 weeks with linezolid at a dose of 1200 mg daily for 26 weeks or 9 weeks or linezolid at a dose of 600 mg daily for 26 weeks or 9 weeks.

The results showed that efficacy decreased a little with the lower dose — a favorable outcome at the end of treatment was observed in 93% of the participants who received 1200 mg daily for 26 weeks, as compared with 91% who received 600 mg daily for 26 weeks. Further decreases were observed when the duration of linezolid treatment was limited to 9 weeks; a favorable outcome was observed in 89% of the participants who received 1200 mg daily and in 84% of those who received 600 mg daily. The incidences of peripheral neuropathy and myelosuppression also decreased with a reduced linezolid dose and duration, from 38% and 22%, respectively, at 1200 mg daily for 26 weeks, to 13% and 7%, respectively, at 600 mg daily for 9 weeks. The balance between efficacy and safety appeared to occur with 600 mg daily for 26 weeks; 91% of the participants who received that dose had a favorable outcome, and among those participants, 24% had neuropathy and 2% had myelosuppression.

In May 2022, the World Health Organization (WHO) issued a rapid communication concerning treatment for multidrug-resistant and rifampin-resistant tuberculosis.[3] This communication was precipitated by data from the ZeNix trial, data from the ongoing TB-PRACTECAL trial (Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen[s]; ClinicalTrials.gov number, NCT02589782), and by the recently published results of the NEXT trial (An Open-label RCT to Evaluate a New Treatment Regimen for Patients with Multidrug Resistant Tuberculosis).[4] The WHO concluded that a 6-month bedaquiline–pretomanid–moxifloxacin regimen that included linezolid at a dose of 600 mg daily may be used in place of longer regimens in persons older than 14 years of age who have multidrug-resistant or rifampin-resistant tuberculosis, regardless of their human immunodeficiency virus status.

The ZeNix trial findings and the new WHO guidance are major advances for the ever-increasing numbers of persons worldwide who have

drug-resistant tuberculosis. However, they raise fresh challenges for national tuberculosis programs that are responsible for the safe implementation of the new regimens, especially in low-income and middle-income countries. These programs require regimens that are widely available and affordable, contain as few drugs as possible, have minimal side effects, and can effect a sustainable cure in 6 months or less. The prospect of the development of peripheral neuropathy in almost a quarter of persons who receive linezolid at a dose of 600 mg daily for 26 weeks, as the trial data suggest, may be difficult for patients and programs alike.

Goswami and colleagues[5] highlight these difficulties in the first 20 patients who received bedaquiline–pretomanid–linezolid in the United States after its approval by the Food and Drug Administration in August 2019. Linezolid therapy was initiated in 18 of the 20 patients at a dose of less than 1200 mg daily, and peripheral neuropathy developed in 6 patients, although 18 patients had undergone therapeutic drug monitoring to attain therapeutic levels of linezolid while minimizing toxic effects.

The priority now is to find a better balance between the efficacy of the new regimens and the toxic effects associated with prolonged linezolid treatment. Strategies that reduce the dose of linezolid to 300 mg daily at or before 16 weeks, as those explored in TB-PRACTECAL, may preserve efficacy with fewer toxic effects.

More sustainable solutions, however, may come from the pipeline of new antituberculosis drugs.[6] Sutezolid and delpazolid are next-generation oxazolidinones that may provide efficacy that is equivalent to that of linezolid, with fewer toxic effects.[7,8] Both drugs are the subject of active trials (SUDOCU [Panacea Sutezolid Dose-finding and Combination Evaluation], NCT03959566; and DECODE [Panacea Delpazolid Dose-finding and Combination Development], NCT04550832). These trials are evaluating the safety, side-effect profiles, pharmacokinetics, and exposure–response relationships of various doses of sutezolid or delpazolid administered for 3 or 4 months with bedaquiline–delamanid–moxifloxacin in adults with drug-sensitive pulmonary tuberculosis. Trial data, which may be available by early 2023, may support the further assessment of these drugs as safe replacements for linezolid in the treatment of drug-resistant and drug-sensitive tuberculosis. In the meantime, as programs adopt linezolid-containing regimens for the treatment of drug-resistant tuberculosis globally, the real-world evaluation of these regimens under programmatic conditions is essential if an acceptable balance between efficacy and safety is to be found.

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1. Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med 2020;382:893-902.
2. Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. N Engl J Med 2022;387:810-23.
3. World Health Organization. Rapid communication: key changes to the treatment of drug-resistant tuberculosis. May 2, 2022 (https://www.who.int/publications/i/item/WHO-UCN-TB-2022-2).
4. Esmail A, Oelofse S, Lombard C, et al. An all-oral 6-month regimen for multidrug-resistant tuberculosis: a multicenter, randomized controlled clinical trial (the NExT study). Am J Respir Crit Care Med 2022;205:1214-27.
5. Goswami ND, Ashkin D, Haley CA. Pretomanid in the treatment of patients with tuberculosis in the United States. N Engl J Med 2022;387:850-2.
6. Butler MS, Gigante V, Sati H, et al. Analysis of the clinical pipeline of treatments for drug-resistant bacterial infections: despite progress, more action is needed. Antimicrob Agents Chemother 2022;66(3):e0199121.
7. Wallis RS, Dawson R, Friedrich SO, et al. Mycobactericidal activity of sutezolid (PNU-100480) in sputum (EBA) and blood (WBA) of patients with pulmonary tuberculosis. PLoS One 2014;9(4):e94462.
8. Kim JS, Kim YH, Lee SH, et al. Early bactericidal activity of delpazolid (LCB01-0371) in patients with pulmonary tuberculosis. Antimicrob Agents Chemother 2022;66(2):e0168421.

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