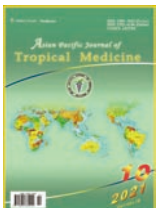

Perspective

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Nix-TB and ZeNix trials: Paving the way for shorter regimens for drug-resistant tuberculosis

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Drug-resistant tuberculosis (DR-TB) continues to be a public health concern. In 2019, nearly half a million patients had rifampicin-resistant tuberculosis (RR-TB), with 78% of those having multidrug-resistant TB (MDR-TB). India (27%), China (14%), and the Russian Federation (8%) are the three countries with the highest share of the global burden. MDR/RR-TB was found in 3.3% of new TB infections and 17.7% of previously treated cases worldwide in 2019[1]. Patients with RR-TB or MDR-TB are treated with a different combination of second-line drugs, usually for 18 months or more. Attempts to reduce the length of conventional MDR-TB regimens and use a combination of tolerable medications have been ongoing for several years through various studies. The successful development of two new anti-TB drugs, bedaquiline and pretomanid, represents a significant step forward in pursuing pan-tuberculosis regimens fit for the 21st century.

Nix-TB was a prospective study of a regimen of bedaquiline (400 mg daily for two weeks followed by 200 mg 3 times a week), pretomanid (200 mg per day) and linezolid (1 200 mg per day starting dose, with dose modifications allowed after the first month), given orally for six months for extensively drug-resistant (XDR) or treatment intolerant or failed MDR-TB. Among 109 TB patients, 98 (90%) had a favourable outcome. Categorically, 89% of XDR TB patients and 92% of non-responsive or treatment intolerant MDR-TB patients had a favourable treatment outcome. The trial concluded that the combination of bedaquiline, pretomanid and linezolid (BPal) led to a favourable outcome, six months after the end of therapy in a high percentage of patients with highly drug-resistant forms of tuberculosis[2]. The regimen further showed an 88% favourable outcome at 24 months post-treatment follow-up[3].

The study found that linezolid was associated with peripheral neuropathy (81%) and myelosuppression (48%), often leading to linezolid dose reduction or treatment interruption. Overall, only 18 patients (17.3%) in the Nix-TB study completed an entire course of linezolid at the 1 200 mg dose, whereas 38 (36.5%) completed with a 600 mg dose, 16 (15.4%) completed with a 300 mg dose and 32 (30.7%) stopped linezolid early due to an adverse event[4]. However, even though neuropathy from linezolid was common but improved over 24 months of follow-up[4]. The experience of the Nix-TB study suggested that it would be necessary to modify the dose of linezolid during treatment based on adverse events.

The pretomanid product label recommends that if either bedaquiline or pretomanid tablets are discontinued, the entire BPaL regimen should also be discontinued. If linezolid is permanently discontinued during the initial four consecutive weeks of treatment, bedaquiline and pretomanid should also be discontinued. If linezolid is discontinued after the initial four weeks of consecutive treatment, clinicians should continue administering bedaquiline and pretomanid, consistent with the Nix-TB study protocol[4]. There is no provision for the replacement of drugs in the BPaL regimen in case of drug resistance or intolerance to any of the drugs used in the regimen.

Thus, additional study to assess linezolid's optimal dosing and duration to treat drug-resistant TB is extremely important[5]. In such a scenario, the ZeNix trial was designed as a successor to the Nix-TB trial. The ZeNix trial enrolled patients with highly resistant TB and treated them for six months with bedaquiline, pretomanid and varying doses and durations of linezolid (BPaL Regimen). Patients were treated for six months with bedaquiline (200 mg daily for eight weeks followed by 100 mg daily for 18 weeks), pretomanid (200 mg daily) and were equally randomized, dose-blinded, to daily linezolid starting at 1200 mg for six months (1 200L6M), 1 200 mg for two months (1 200L2M), 600 mg for six months (600L6M), or 600 mg for two months (600L2M). A total of 181 participants of highly resistant TB were enrolled. A high success rate at the primary endpoint, like Nix-TB, was observed:

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93% in 1 200L6M, 89% in 1 200L2M, 91% in 600L6M and 84% in 600L2M. Peripheral neuropathy and myelosuppression were seen in 38% and 22% in 1 200L6M, 24% and 17% in 1 200L2M, 24% and 2% in 600L6M, and 13% and 7% in 600L2M, respectively[6].

Thus, the ZeNix trial has, for the first time, provided us with clinical evidence to support reduced dosing or duration of linezolid in the BPaL regimen.

Nix-TB and ZeNix trials are the landmark trials towards shortening the duration and number of drugs used to treat drug-resistant TB. Thus, they will revolutionize the future of shorter regimens for drug-resistant TB. These regimens need to be reserved only for drug-resistant pulmonary tuberculosis patients and not for extrapulmonary TB patients. These regimens' inclusion and exclusion criteria should be strictly based on the Nix-TB and ZeNix trial criteria. Any loss to follow up or poor adherence/compliance to these regimens may be catastrophic. The emergence of drug resistance to the drugs used in these regimens may be detrimental to drug-resistant TB treatment outcomes in the near future. This is especially important as currently, the facilities for sensitivity testing of the drugs used in the BPaL regimen are limited; hence, there will be a substantial delay in picking up resistance to these drugs if they develop in the near future. Therefore, careful patient selection is the key to the success of these regimens, and these regimens should be implemented only as standardized treatments under programmatic conditions with strict monitoring.

In a developing country like India, 70%-80% of first contact care of TB patients happens in the private sector, and the diagnostic and treatment practices pertaining to tuberculosis control in the private sector are largely suboptimal[7]. Incorrect TB prescriptions are a considerable hurdle in delivering effective TB treatment to patients in such settings. In addition, loss to follow-up is a significant problem adversely affecting the treatment outcomes of these TB patients. In such a scenario, a major challenge would be to prevent incorrect prescription of the shorter regimens for drug-resistant TB and ensure good compliance of patients towards these regimens, especially in the private sector.

A good public-private mix in implementing these regimens will be the key to increasing the number of TB patients benefiting from these regimens and increasing the success of these regimens among drug-resistant TB patients[7]. A rapid capacity building of drug sensitivity testing facilities for the second-line anti-TB drugs being used in the BPaL regimen is also essential to check resistance to any drugs used in the regimen. These are crucial issues that need to be addressed before rolling out the new shorter DR-TB drug regimen.

Future research must develop diagnostics and therapeutics directed towards shorter DR-TB regimens with greater efficacy and least toxicity. Tools, especially rapid molecular assays for monitoring resistance to the drugs used in the BPaL regimen, need to be developed at a fast pace. Predictable toxicities and the emergence of resistance are directly related to continuing efforts to produce new regimens such as the BPaL, and boosting such research is urgently needed.

A shorter regimen for drug-resistant TB will improve compliance as it reduces the duration and the number of adverse events, which ultimately translate to improvement in treatment success rate. Thus, adopting newer, shorter regimens for drug-resistant TB based on these results will benefit the drug-resistant TB patients and national TB programs across the globe.

Conflict of interest statement

The author declares that there is no conflict of interest.

References

[1] World Health Organization. *Global tuberculosis report 2020. Geneva, Switzerland, 2020.* [Online]. Available from: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf. [Accessed on 30 September 2021].

[2] Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* 2020; **382**: 893-902. doi: 10.1056/NEJMoa1901814.

[3] Conradie F, Diacon A, Ngubane N, Everitt D, Crook AM, Wills G, et al. Final results of the Nix-TB clinical study of BPal regimen for highly resistant TB. *Presented at CROI: Conference on Retroviruses and Opportunistic Infections*. Virtual, 2021.

[4] World Health Organization. *WHO consolidated guidelines on tuberculosis, Module 4: Treatment-drug-resistant tuberculosis treatment. Online annexes*. [Online]. Available from: https://apps.who.int/iris/rest/bitstreams/1280998/retrieve [Accessed on 30 September 2021].

[5] Wang MC, Cervantes J. Glycemic control in tuberculosis: Lessons learned from Taiwan. *Asian Pac J Trop Med* 2019; **12**(10): 438-441.

[6] Conradie F, Everitt D, Olugbosi M, Wills G, Fabiane S, Timm J, et al. High rate of successful outcomes treating highly resistant TB in the ZeNix study of pretomanid, bedaquiline and alternative doses and durations of linezolid. In: *IAS 2021-the 11th IAS Conference on HIV Science*, 18-21 July 2021, Berlin, Germany. [Online]. Available from: https://www.ias2021.org/wp-content/uploads/2021/07/IAS2021_Abstracts_web.pdf. [Accessed on September 30 2021].

[7] Mishra GP. Public-private mix in tuberculosis. *Lancet Infect Dis* 2012; **12**(12): 908-909.