Indian J Med Res 154, July 2021, pp 16-18
DOI: 10.4103/ijmr.IJMR_3537_20

Quick Response Code:

Commentary

Linezolid-resistant *Mycobacterium tuberculosis*: Will it impact the tuberculosis elimination programme?

The spread of drug-resistant tuberculosis (TB) is a cause for global concern, and the control of TB is hampered by the emergence of multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB) and now the totally drug-resistant (TDR) TB or XXDRTB, *i.e*. extremely drug-resistant TB. This has emerged in China, India, Africa and Eastern Europe[1]. India alone is responsible for 27 per cent of the global burden of MDR-TB[2]. Drug resistance in TB remains a human-made phenomenon. Non-compliance, erratic compliance and treatment mismanagement are the predominant reasons for the spread of MDR and XDR TB. Acquired drug resistance to isoniazid and rifampicin and some second-line drugs is common in India. XDR-TB patients in India comprise 0.3-30 per cent of drug-resistant TB[3,4].

There are currently limited treatment strategies available to manage XDR-TB. Physicians often need to fall back on newer drugs to make up the minimum number of active drugs required to ensure a successful regimen. To this end, linezolid (LZD), an oxazolidinone, initially used for the treatment of drug-resistant Gram-positive bacterial infections has been repurposed for the treatment of XDR-TB[5]. The role of LZD in the treatment of MDR and XDR-TB has been controversial despite its excellent pharmacological properties against *Mycobacterium tuberculosis*. A systematic review and meta-analysis in 2012 demonstrated that treatment success was achieved in the majority of the patients on LZD[6].

The safety profile of LZD made many treating physicians reluctant to use this drug in patients where better drugs were available[7]. The toxicity of the drug was due to the drug binding to human mitochondria, inhibiting protein synthesis and thus resulting in toxicity in clinical use[8]. Although serious concerns about the safety profile of LZD were expressed, a study from India showed that it was an effective, cost-effective, and relatively safe drug. It also improved the outcomes in drug-resistant TB[9]. Subsequently, it was recommended as a preferred agent for the treatment of patients with drug-resistant TB by the WHO in 2019 and classified as a Group A drug[5].

The introduction of LZD in the management of drug-resistant TB has resulted in better treatment outcomes, however, the emergence of resistance to this drug warrants the monitoring of clinical isolates of *M. tuberculosis* for their sensitivity to LZD[10]. A regimen containing bedaquiline, pretomanid and LZD is, thus, often recommended for the treatment of XDR-TB patients[1].

Nambiar *et al*[10] in this issue performed whole genome sequencing (WGS) to identify mutations associated with LZD resistance in phenotypically LZD-resistant clinical isolates of *M. tuberculosis*. They identified the presence of C154R in the *rplc* gene and G2814T in the *rrl* gene as the major resistance determinants. LZD-resistance was first reported in 2007[11], but the data on its resistance in TB are still scarce. The largest series reported to date is from South Africa, in which 39 patients with treatment failure were documented and their isolates were shown to be LZD resistant[12]. In India, to date LZD-resistant *M. tuberculosis* clinical strains still seem to be rare. The first published report was from Mumbai in 2017, where the authors reported one per cent resistance rate to LZD among isolates from MDR-TB patients[13]. The emergence in resistance to this critical drug will result in a decrease in the repertoire of drugs available for the management of drug-resistant TB. This problem will be compounded by the fact that the drug shares key binding sites and displays cross-resistance with other oxazolidinones, including those in the pipeline such as sutezolid and delpazolid[12].

Usually, LZD resistance has been reported only after prolonged exposure to the drug, but it could occur spontaneously even without exposure to the drug[14]. A drug regimen which is already suboptimal at the time of addition of LZD would result in LZD acting like a monotherapy over prolonged periods and thus precipitate the development of resistance. As LZD resistance increases, it is likely to be associated with increased mortality. Hence, there is a need for early inclusion of other drugs along with it such as bedaquiline to reduce the risk of treatment failures.

Phenotypic drug sensitivity testing for LZD should be performed for all isolates from drug-resistant TB patients with treatment failures. This is usually done by estimating its minimum inhibitory concentration (MIC) by microbroth dilution methods and resistance identified if the MIC of the clinical isolate is >1 mg/l[10]. Genotyping mutations in association with LZD resistance are usually seen in 23S rRNA leading to MIC elevations and clinical resistance[8]. Strains showing low level of resistance, *i.e*. with MICs of 4-8 µg/ml, often show no mutations, while those with higher MICs usually show a mutation in the 23S rRNA. Thus, often phenotypically resistant isolates are reported, which do not yield any mutations[8]. Resistance without genetic mutation could be due to other mechanisms such as the involvement of efflux pumps or decreased permeability of the mycobacterial cell wall[8]. More studies are required on the role of efflux pumps and porins in the development of clinical drug resistance to LZD.

Mutants with reduced bacillary susceptibility to LZD usually harbor *rrl* and *rplC* mutations[14]. Mutations in *rplC* gene are associated with higher LZD MIC values (MICs of >2 g/ml), whereas mutations in *rrl* gene correlate with lower MIC values[15]. The common mutations reported to be associated with *rrl* gene are at positions 2061 and 2057[10]. Substitutions at G2814T, A2810C, G2746A, G2270 and a few other mutations have also been reported in the *rrl* gene[11,12]. The T460C mutation is commonly seen in the *rplC* gene. Other mutations reported in this gene are C154R and A328G[12,15]. The sequence mixes in *rrl* and *rplC* have so far shown low diversity and a limited number of mutations have been seen to be associated with LZD resistance[12]. This raises the possibility of translation of such data into rapid molecular diagnostics. Molecular testing could also be class-based because of cross-resistance with other oxazolidinones and would have the advantage of early identification of resistance.

It is, thus, necessary to undertake comparative analysis of genotypic and phenotypic findings and compile a list of high-confidence mutations associated with LZD resistance. In fact, as more and more novel drugs are introduced in the treatment of TB, these must be monitored regularly by phenotypic susceptibility testing and determination of genetic mutations associated with resistance[5].

Increased vigilance and active surveillance are needed for emerging resistance to LZD, as this is likely to impact the National TB Elimination Programme (NTEP). Regular monitoring of phenotypic resistance of isolates from different parts of the country and determination of genetic mutations conferring resistance should thus be an ongoing programme. To summarize, a better understanding of the clinical predictors and genotypic correlates of LZD resistance is critical to devise strategies to preserve this important anti-TB agent to eradicate TB.

***Conflicts of Interest*:** None.

Renu Bharadwaj
Department of Microbiology, B.J. Government Medical College, Pune 411 038, Maharashtra, India
renu.bharadwaj@gmail.com

Received August 18, 2020

References

1. Lacobino A, Fattorini L, Giannoni F. Drug-resistant tuberculosis 2020: Where we stand. *Appl Sci* 2020; *10* : 2153-70.
2. Ministry of Health & Family Welfare. *National strategic plan to end tuberculosis in India 2020-2025*. Available from: *https://www.tbcindia.gov.in/*, accessed on July 17, 2020.
3. Ramachandran R, Nalini S, Chandrasekar V, Dave PV, Sanghvi AS, Wares F, *et al*. Surveillance of drug-resistant tuberculosis in the state of Gujarat, India. *Int J Tuberc Lung Dis* 2009; *13* : 1154-60.
4. Prasad R, Singh A, Balasubramanian V, Gupta N. Extensively drug-resistant tuberculosis in India: Current evidence on diagnosis & management. *Indian J Med Res* 2017; *145* : 271-93.
5. World Health Organization. *WHO consolidated guidelines on drug-resistant tuberculosis treatment*. Geneva, Switzerland: WHO; 2019.
6. Sotgiu G, Centis R, D'Ambro*sio* L, Alffenaar JW, Anger HA, Caminero JA, *et al.* Efficacy, safety and tolerability of linezolid

containing regimens in treating MDR-TB and XDR-TB: Systematic review and meta-analysis. *Eur Respir J* 2012; *40* : 1430-42.

7. Migliori GB, Eker B, Richardson MD, Sotgiu G, Zellweger JP, Skrahina A, *et al*. A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. *Eur Respir J* 2009; *34* : 387-93.
8. Singh B, Cocker D, Ryan H, Sloan DJ. Linezolid for drug-resistant pulmonary tuberculosis. *Cochrane Database Syst Rev* 2019; *3* : CD012836.
9. Singla R, Camineron JA, Jaiswal A, Singla N, Gupta S, Bal RK, *et al*. Linezolid: An effective, safe and cheap drug for patients failing multidrug-resistant tuberculosis treatment in India. *Eur Respir J* 2012; *39* : 956-62.
10. Nambiar R, Tornheim JA, Diricks M, Bruyne KD, Sadani M, Shetty A, *et al*. Linezolid resistance in *Mycobacterium tuberculosis* isolates at a tertiary care centre in Mumbai, India. *Indian J Med Res* 2021; *154* : 85-9.
11. Richter E, Rüsch-Gerdes S, Hillemann D. First linezolid-resistant clinical isolates of *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 2007; *51* : 1534-6.
12. Wasserman S, Louw G, Ramangoaela L, Barber G, Hayes C, Omar SV, *et al*. Linezolid resistance in patients with drug-resistant TB and treatment failure in South Africa. *J Antimicrob Chemother* 2019; *74* : 2377-84.
13. Tornheim J, Ganatra S, Deluca A, Banka R, Rodrigues C, Gupta A, *et al*. Linezolid experience among MDR-TB patients in Mumbai. *Eur Respir J* 2017; *50* (Suppl 61) : PA3486.
14. Yang JS, Kim KJ, Choi H, Lee SH. Delamanid, bedaquiline, and linezolid minimum inhibitory concentration distributions and resistance-related gene mutations in multidrug-resistant and extensively drug-resistant tuberculosis in Korea. *Ann Lab Med* 2018; *38* : 563-8.
15. Zhang S, Chen J, Cui P, Shi W, Shi X, Niu H, *et al*. *Mycobacterium tuberculosis* mutations associated with reduced susceptibility to Linezolid. *Antimicrob Agents Chemother* 2016; *60* : 2542-4.