Journal of Infection and Public Health 17 (2024) 172–174

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: www.elsevier.com/locate/jiph

Review

Role for Linezolid in drug sensitive tuberculosis

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ARTICLE INFO

Article history:
Received 8 May 2023
Received in revised form 29 September 2023
Accepted 8 November 2023

Keywords:
Linezolid
Drug-sensitive tuberculosis
Resistant tuberculosis
Clinical trial

ABSTRACT

Tuberculosis (TB) continues to be a global challenge. Reducing the duration of TB treatment for drug-sensitive TB (DSTB) has direct and distinct advantages. We ventured into the aspect of utilizing linezolid as a pivotal drug in shortening therapy in DSTB. Linezolid has gained prominence as it is faring well in resistant TB management. Only a few studies use the strategy of Linezolid in DS-TB but it seems a lucrative approach, the bactericidal effects have been reported favourably in the studies. There have been concerns about the potential adverse drug effects of Linezolid reported but clinical trials have demonstrated safety and tolerability when administered for shorter periods. If the safety and efficacy of giving Linezolid for a shorter period along with standard drugs for DSTB is established it could lead to newer avenues using Linezolid for shortening the duration of treatment for DSTB as an alternative to treat DSTB.

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Introduction

Tuberculosis (TB) continues to be a global challenge with India continuing its fight to lower its high TB burden, as it marches towards the goal of achieving its target of TB elimination by 2025. The standard treatment for drug-sensitive TB (DSTB) had remained a regimen of 6 months of INH and rifampicin fortified with pyrazinamide and ethambutol in the intensive phase of 2 months. Recently, both in the World Health Organization (WHO) and National Tuberculosis Elimination Program (NTEP), India guidelines, ethambutol has been continued in the continuation phase due to the higher prevalence of INH resistance in the community that could adversely affect TB outcomes [1]. Reducing the duration of TB treatment for DSTB has direct and distinct advantages making it a lucrative strategy in all forms of TB, with better completion and lower attrition rates. From 12–18 months of therapy, the duration has considerably reduced to 6 months over two decades with evidence generated by trials conducted globally as well as from our Institute, with the world shifting its focus towards reducing the duration further, with the expectation of more compliance among TB patients to achieve better completion rates. Likely, cumulative toxicity, pill burden and cost will also be simultaneously reduced making it programmatically and economically a feasible strategy.

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https://doi.org/10.1016/j.jiph.2023.11.012

As long-term efficacy is determined by the reduction of TB recurrences, dictated primarily by the subpopulation of TB bacilli termed "persistors", only those drugs that are bactericidal, as well as sterilicidal drugs, can help eliminate persistors and find a place in shorter TB regimens. Linezolid, with these desirable attributes, has rightfully entered into many global trials, like the TRUNCATE trial [2]. Analogues like sutezolid, delpazolid and Tedizolid have a wider spectrum, better efficacy along with lesser myelosuppression that is gaining popularity and global interest. In this context, we propose to venture into the aspect of looking at linezolid and its pivotal role in shortening therapy in drug-sensitive TB. We reviewed the literature and prepared a narrative review that did not involve any human subjects, approval from the Institutional Ethics Committee was not required, however, it was approved by the Institutional Manuscript Committee as well as the Research Integrity Committee, of the institute as an institutional policy.

Methodology of the search strategy: We used the terms "Linezolid" AND "drug-sensitive tuberculosis" (OR drug-susceptible) AND "clinical trial" in the PubMed search to include the clinical trials and exclude other types and that led to few clinical trials. This search process was done in June 2023 and we included the trials conducted and ongoing in the past 10 years. We applied the same in the ClinicalTrials.gov website of the United States NIH clinical trials registry database and used the same terms, that yielded 21 hits. However, the DSTB trials that used Linezolid in their trials, yielded only 5 clinical trials. We used the terms "Linezolid" AND "drug-sensitive tuberculosis" AND "review" in the PubMed search to understand how many reviews were written up and that yielded 3 reviews. We also used the terms "Linezolid" AND "drug-resistant tuberculosis" AND "effectiveness" to understand the DRTB studies where Linezolid was used.

The prowess of linezolid in resistant TB (DR-TB)

Linezolid has gained prominence as it is figured as a Group A drug in resistant TB management. According to a rapid communication from the World Health Organization (WHO) in 2018, linezolid can be used for all patients with multi-drug resistant TB (MDR-TB) except when contraindicated clinically. [3] In May 2022, the WHO issued a rapid communication [4] recommending that the 6-month BPaLM regimen, which includes bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin, be used programmatically in patients with MDR/Rifampicin Resistant -TB who have not previously received bedaquiline, pretomanid, or linezolid (defined as > 1-month exposure). According to the prior guidelines, these patients were treated with 9-month or longer (> 18-month) regimens. In the case of documented fluoroquinolone resistance (in patients with pre-XDR-TB), this regimen can be administered without moxifloxacin (BPaL). Linezolid has been demonstrated to be effective, inexpensive, and generally safe for MDR-TB patients in India, including those with confirmed pre-XDR or XDR-TB [5].

Systematic reviews showed that Linezolid (LZD) has been effective against drug-resistant tuberculosis [6–8]. When Linezolid was used in their treatment regimen, the pooled proportion for treatment success was 77.36% (95% CI = 71.38–82.83%) and the culture conversion rate was 88.45% (95% CI = 83.82–92.38%), according to a systematic review and meta-analysis of twenty-three studies[6]. Only myelosuppression had a significant association with toxicity, and that increased with dosage proportionately. ($p < 0.0001$). Another systematic review [7] that included twenty-two studies found that the pooled estimates for sputum culture conversion and treatment success rates in XDR-TB patients on LZD-containing regimens were 93.2% and 67.4% respectively. The meta-analysis of the rate of adverse events such as myelosuppression, peripheral neuropathy, optic neuritis, and gastrointestinal tract adverse reactions was found to be 42.5%, 26% 19%, and 35%, respectively. However, those who received a higher initial dose (> 600 mg/day) of LZD were found to have an increased proportion of myelosuppression (48.4% vs. 24.8% P = 0.01) and gastrointestinal adverse effects (41.3% vs. 15.4%, P = 0.100) compared to those receiving lower doses (< =600 mg/day). A Cochrane review revealed there was low certainty of evidence on the efficacy of linezolid for drug-resistant pulmonary TB from randomized controlled trials in patients with XDR-TB [8].

Linezolid in DSTB

There are very limited studies that have worked and are working with Linezolid in drug-susceptible tuberculosis [2,9–12]. Searching the clinical trials on DSTB on the NIH Clinical Trials website yielded only five studies either ongoing or completed [13]. Investigators randomized newly diagnosed DSTB patients into one of six arms containing linezolid at 300 mg once daily, 300 mg twice daily, 600 mg QD, 600 mg BD, 1200 mg QD, 1200 mg three times per week (TIW), or a combination of isoniazid, rifampin, pyrazinamide, and ethambutol given for 14 days to study fourteen-Day bactericidal activity, safety, and pharmacokinetics of Linezolid [9]. Importantly, in the TRUNCATE trial, published study findings [13] show that the linezolid-containing regimen given for eight-week duration had established non-inferiority to the standard treatment. The antimycobacterial activity was shown to be favourably correlated with plasma drug exposure and percentage time over MIC, with no unanticipated adverse effects, and all linezolid dosages had good bactericidal activity. Linezolid has also been shown to have early bactericidal activity even in patients with cavitary PTB. It was demonstrated as early as two days of administration in a randomised trial when the newly diagnosed bacteriologically confirmed PTB were assigned to receive a daily dose of 300 mg isoniazid and twice daily or a once-daily dose of 600 mg of linezolid for seven days [10].

The less tolerable linezolid in the long run

As reported in the previous sections, there had been a concern about the potential adverse drug effects of Linezolid reported by studies using Linezolid for treating Tuberculosis. Clinical trials have demonstrated that linezolid is generally safe and well-tolerated when administered for short periods [13]. So it is clear that there is a possibility of ensuring safety when Linezolid is given for a shorter duration. Evidence from the Nix-TB trial [14] and ZeNix trial [15] that studied shorter DR-TB regimens have demonstrated that the reduction of the duration of the Linezolid during TB treatment has ensured better safety.

Discussion

Linezolid is effective against resistant TB but with limited information on its usage in drug-sensitive TB. As it is established that Linezolid is effective in resistant TB, it should work in DSTB as well. Hence from a public health point of view, using Linezolid in drug-sensitive tuberculosis is likely to provide the benefits of reducing the duration of DSTB treatment, thereby reducing the cost of the TB treatment. Thus there could be an improvement in treatment adherence which could lead to a reduction of development of drug resistance. Linezolid is effective, safer and cheaper especially in countries like India [5] where the TB burden is high, so it is important to utilize the option.

There is evidence from the Zenix trial that lesser dosages and shorter duration make the Linezolid drug safer, which is also demonstrated by the TRUNCATE trial. In the TRUNCATE trial, the group assigned to receive linezolid containing regimen along with Bedaquiline was the only group that met the non-inferiority criteria, concluding the efficacy and safety. The trial however had used Bedaquiline along with the Linezolid, but we suggest retaining the

Bedaquiline for DR-TB and using Linezolid along with the first-line drugs to have the desired outcome.

We presume that Linezolid for DSTB given for 2 weeks to 8 weeks, along with other standard drugs, namely Rifampicin, INH, Ethambutol and Pyrazinamide is presumed to shorten TB treatment for a duration shorter than six months. If the safety of giving Linezolid for a shorter period along with standard drugs for DSTB is well established, subsequent efficacy evaluation could lead to newer avenues for shortening the duration of treatment for DSTB using Linezolid and we suggest such clinical trials must be encouraged and pursued. This could very well preserve the newer anti-TB drugs like Bedaquiline, Delamanid, and Pretomanid to be sparingly used exclusively for treating pre-XDR and XDR TB. WHO has said in the research priorities listed in the TB treatment guidelines 2017 for Drug Sensitive TB [16], to explore the effectiveness of Fluoroquinolones that needs to be evaluated in different sub-groups and the reason for evaluation of relapse when it was used in the DSTB regimens. We suggest instead of fluoroquinolones, Linezolid would be a suitable alternative as a surgical strike in the initial period, devoid of side effects that may crop up with sustained usage. It is to be noted that Fluoroquinolones, through established contenders in treatment shortening, require a full course to be given for at least 4 months to achieve optimal results.

Conclusion

Linezolid being effective against resistant TB, it may be used in drug-sensitive TB as an alternative regimen but may be given for a shorter duration of four to eight weeks owing to safety concerns. There is an urgent need to conduct clinical trials using Linezolid for DSTB to establish substantial evidence regarding its safety and efficacy and to capitalise on this drug for effectively shortening TB treatment understanding its mycobacterial activity against persistors and its inherent potency to curb TB recurrences despite the shorter duration of treatment.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or Not-for-profit sectors.

Declaration of Competing Interest

The authors declare nil conflict of interest.

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