Letter to the Editor

trd Tuberculosis & Respiratory Diseases

Treatment Outcomes of Fluoroquinolone-Resistant Multidrug-Resistant Tuberculosis: An Implication for Delamanid - Authors' Reply

https://doi.org/10.4046/trd.2024.0010
ISSN: 1738-3536(Print)/
2005-6184(Online)
Tuberc Respir Dis 2024;87:209-211

Saerom Kim, M.D.[1,2] and Jeongha Mok, M.D., Ph.D.[1,2,3]

[1]Department of Internal Medicine, [2]Biomedical Research Institute, Pusan National University Hospital, Busan, [3]Department of Internal Medicine, Pusan National University School of Medicine, Busan, Republic of Korea

Check for updates

Copyright © 2024 The Korean Academy of Tuberculosis and Respiratory Diseases

Address for correspondence
Jeongha Mok, M.D., Ph.D.
Department of Internal Medicine, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, Republic of Korea
Phone 82-51-240-7889
Fax 82-51-254-3127
E-mail mokgamokga@gmail.com
Received Jan. 20, 2024
Accepted Jan. 24, 2024
Published online Jan. 30, 2024

This is identical to the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/).

We express our gratitude to Putra and Purnamasari for their comments on our article, which explored the impact of anti-tuberculosis (TB) drug use on treatment outcomes in patients with pulmonary fluoroquinolone-resistant multidrug-resistant tuberculosis (FQr-MDR-TB)[1]. Fluoroquinolones (FQs) have been core drugs in the treatment of MDR-TB for many years due to their superior bactericidal and sterilizing properties and their role in preventing resistance to other anti-TB drugs[2]. However, the broad use of FQs in treating conditions such as pneumonia and urinary tract infections, along with their extensive application in MDR-TB treatment, has led to an increase in FQ resistance among TB patients. This resistance complicates the formulation of effective treatment regimens for FQr-MDR-TB, resulting in less favorable outcomes compared to those observed in patients with fluoroquinolone-susceptible-MDR-TB (FQs-MDR-TB)[3]. Therefore, as recommended by Putra and Purnamasari, it is necessary to consider new anti-TB drugs, such as delamanid (DLM), for patients with FQr-MDR-TB to improve the efficacy and effectiveness of treatment regimens.

In our study, the use of DLM did not significantly affect treatment success or reduce mortality in patients with FQr-MDR-TB[1]. This apparent lack of efficacy might be more attributable to the greater severity of TB in patients treated with DLM than to the reduced effectiveness of the drug itself. During the study period in South Korea, DLM was prescribed primarily for patients who could not use conventional anti-TB drugs due to high-level resistance or severe adverse events, or for those with extensive lung destruction, which generally indicates a poor prognosis. Notably, in our study, patients receiving DLM showed greater resistance to other anti-TB drugs and were older compared to those not treated with DLM. Despite rigorous efforts to minimize confounding factors through propensity score matching and multivariate analyses, we acknowledge that it might not have been possible to fully adjust for all of these confounding elements statistically.

DLM, a nitro-dihydro-imidazooxazole derivative, exhibits anti-TB properties by inhibiting the synthesis of mycolic acid, a crucial component of the *Mycobacterium tuberculosis* cell wall. DLM has shown promising bactericidal and sterilizing activity against *M. tuberculosis* in preclinical studies. It received approval as an anti-TB drug for treating MDR-TB, based on its ability to accelerate culture conversion and its excellent treatment outcomes in phase 2 and subsequent follow-up studies[4,5]. Unfortunately, DLM did not meet the primary outcome in a later phase 3 trial[6]. Following this, a World Health Organization (WHO) meta-analysis did not find significant improvements in outcomes for MDR-TB patients treated with DLM, leading

to its exclusion from the WHO's list of core drugs for longer MDR-TB treatment regimens[7]. It is important to note that DLM entered clinical practice after bedaquiline (BDQ), resulting in comparatively less clinical experience at the time of the WHO analysis. Additionally, DLM's inclusion in the WHO meta-analysis was limited, both in terms of the number of patients treated and the clinical trials conducted. Thus, the decision regarding DLM's role in MDR-TB treatment is based on relatively limited evidence.

However, experience with and evidence for DLM continues to accumulate in real-world practice and ongoing clinical trials. Several global studies have reported that DLM improves treatment outcomes in patients with MDR-TB, pre-extensively drug-resistant (pre-XDR)-TB, and XDR-TB, without significant concerns over tolerability or safety[8,9]. The combined use of DLM and BDQ in patients with highly resistant MDR-TB has also been reported as effective and safe[10]. A recent study from South Korea, comparing treatment outcomes and adverse events in MDR-TB patients treated with either BDQ or DLM, revealed no statistically significant differences between the groups[8].

Recently, the WHO, in its updated guidelines, recommended prioritizing various shorter regimens over longer regimens for the treatment of MDR-TB[11]. The treatment approach for MDR-TB is evolving toward shorter, more convenient, and safer all-oral regimens. In this evolving context, the efficacy of DLM has been demonstrated in several clinical trials evaluating shorter regimens for MDR-TB. A 9-month regimen that includes DLM, levofloxacin, linezolid, and pyrazinamide (the "MDR-END regimen") for patients with FQs-MDR-TB showed non-inferior treatment outcomes compared to the longer 20- to 24-month regimens[12,13]. Additionally, a 6- to 9-month regimen consisting of DLM, BDQ, linezolid, and clofazimine (the "BEAT-India regimen") for MDR-TB patients with additional resistance to FQs or second-line injectables achieved an overall favorable outcome rate of 91%[14]. Furthermore, clinical trials investigating various shorter regimens containing DLM are ongoing, with promising results expected.

In conclusion, while further evidence may be necessary, as indicated by Putra and Purnamasari, DLM could be a viable and safe option for treating MDR-TB, pre-XDR-TB, and XDR-TB. Given the increasing global experience with the use of DLM and the ongoing publication of clinical trial results on various shorter regimens that include DLM, re-evaluation of the role of DLM in MDR-TB treatment is warranted.

Authors' Contributions

Conceptualization: Mok J. Writing - original draft preparation: all auhors. Writing - review and editing: all auhors. Approval of final manuscript: all auhors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Funding

No funding to declare.

References

1. Choi H, Jeong D, Kang YA, Jeon D, Kang HY, Kim HJ, et al. Impact of anti-tuberculosis drug use on treatment outcomes in patients with pulmonary fluoroquinolone-resistant multidrug-resistant tuberculosis: a nationwide retrospective cohort study with propensity score matching. Tuberc Respir Dis (Seoul) 2023;86:234-44.
2. Van Deun A, Decroo T, Piubello A, de Jong BC, Lynen L, Rieder HL. Principles for constructing a tuberculosis treatment regimen: the role and definition of core and companion drugs. Int J Tuberc Lung Dis 2018;22:239-45.
3. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018;392:821-34.
4. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med 2012;366:2151-60.
5. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur Respir J 2013;41:1393-400.
6. von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag V Jr, Ticona E, Segura P, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med 2019;7:249-59.
7. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: WHO; 2019.
8. Hwang H, Kang H, Kwon YS, Jeon D, Shim TS, Yim JJ. Out-

comes of multidrug-resistant tuberculosis treated with bedaquiline or delamanid. Clin Infect Dis 2021;73:1362-9.
9. Mohr E, Hughes J, Reuter A, Trivino Duran L, Ferlazzo G, Daniels J, et al. Delamanid for rifampicin-resistant tuberculosis: a retrospective study from South Africa. Eur Respir J 2018;51:1800017.
10. Huerga H, Khan U, Bastard M, Mitnick CD, Lachenal N, Khan PY, et al. Safety and effectiveness outcomes from a 14-country cohort of patients with multi-drug resistant tuberculosis treated concomitantly with bedaquiline, delamanid, and other second-line drugs. Clin Infect Dis 2022;75:1307-14.
11. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment. Drug-resistant tuberculosis treatment, 2022 update. Geneva: WHO; 2022.
12. Mok J, Lee M, Kim DK, Kim JS, Jhun BW, Jo KW, et al. 9 Months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea. Lancet 2022;400:1522-30.
13. Lee M, Mok J, Kim DK, Shim TS, Koh WJ, Jeon D, et al. Delamanid, linezolid, levofloxacin, and pyrazinamide for the treatment of patients with fluoroquinolone-sensitive multidrug-resistant tuberculosis (Treatment Shortening of MDR-TB Using Existing and New Drugs, MDR-END): study protocol for a phase II/III, multicenter, randomized, open-label clinical trial. Trials 2019;20:57.
14. Padmapriyadarsini C, Vohra V, Bhatnagar A, Solanki R, Sridhar R, Anande L, et al. Bedaquiline, delamanid, linezolid and clofazimine for treatment of pre-extensively drug-resistant tuberculosis. Clin Infect Dis 2022;76:e938-46.