Shortening MDR-TB treatment

Akkerman, O W; Tiberi, S; Alffenaar, J-W

Published in:
International Journal of Tuberculosis and Lung Disease

DOI:
10.5588/ijtld.21.0146

Publication date:
2021

INT J TUBERC LUNG DIS 25(6):419–420

http://dx.doi.org/10.5588/ijtld.21.0146

EDITORIAL

Shortening MDR-TB treatment: is treating more patients with fewer drugs better?

According to the WHO, rifampicin-resistant (RR-), multidrug-resistant (MDR-) and extensively drug-resistant TB (XDR-TB) remain a global health problem.[1] It is concerning that the estimated global burden of MDR-TB has remained constant at half a million cases per year, and the percentage of new cases (an estimated 3.3%) and previously treated cases (estimated at 18%) is not decreasing according to the goals set out in the WHO End TB strategy.[1] In 2018, the first UN High-Level Meeting on TB was held.[2] Among the topics discussed were 5-year targets for patients receiving treatment for MDR/RR-TB. While the target for people receiving treatment were 1.5 million of the estimated 2.5 million cases over a 5-year period,[3] starting treatment regimens for MDR-TB are in only 38% of cases.[1] This explains why average success rates among these patients are still low, around 57% worldwide.[1] However, it is encouraging to note that more successful outcomes of up to 85–90% have been reported.[4] In order to improve treatment outcome challenges such as the detection of drug-resistant cases, efficient distribution of bedaquiline (BDQ) and timely implementation of new shorter oral regimens have to be overcome, especially in high-incidence settings.

Because new drugs and simple treatment regimens are urgently needed, the paper by Oelofse and colleagues in this issue of the *Journal* is timely.[5] The study compares cohorts of two different treatment regimens, BDQ + pretomanid + linezolid (BPaL) vs. a bedaquiline-linezolid (BL) based regimen. Overall treatment outcomes in the original studies were 90% for the BPaL regimen and 66% for the BL cohort. To note, outcome does not appear to be affected by HIV status; a recent study by Padayatchi et al. reported a cure rate of 63% with BDQ-containing regimens in a cohort comprised mainly of people living with HIV.[6] Furthermore, time to culture conversion was significantly shorter for the BPaL regimen. However, a comparisons of both studies should be done with caution due to the differences in the study design and risk of bias. The BL-based regimen study was a prospective programmatic cohort recruited between 2008 and 2017 comprising patients admitted to the designated XDR-TB treatment centre. The BPaL study was an open-label, single-group study, and patients enrolled had failed prior MDR- or XDR-TB treatment.

The original studies that were compared by Oelofse et al.[5] reported that all patients experienced adverse events for the BPaL regimen, whereas 96% in the original BL cohort experienced adverse events;[7,8] 57% of grade 3 or 4 adverse events in the BPaL cohort and 32.7% in the BL cohort were attributed to linezolid (LZD) and 0% to BDQ. This seems high in comparison to a large global study on adverse events in the treatment of MDR-TB showing that 12.9% of the patients experienced adverse events due to LZD, and only 2.8% experienced severe adverse events; 11.1% of the patients had adverse events ascribed to BDQ, and only 1% experienced severe adverse events (grades 3–5).[9] This difference may be due to the higher dose of LZD employed in the BPaL regimen. Another explanation is that adverse events reporting strategies between clinical trials and clinical practice differ.

Improving treatment outcome rates of RR/MDR/XDR-TB needs further work.[10] Fortunately, several randomised controlled studies investigating different treatment regimens are under way [NCT03086486; NCT04717908; NCT03828201; NCT04062201]. Furthermore, interpreting outcome would be easier if appropriate drug susceptibility testing (DST) is performed, and ideally at least a subset of the study population is used to increase knowledge of the pharmacokinetic (PK) properties of the regimens in specific populations.[11] Both DST and PK can help interpreting efficacy and toxicity rates among the study participants.[12]

LZD (a repurposed anti-TB drug) was given at a higher dose in NiX-TB than that used by most other centres and programmes, and may have been the reason for the higher efficacy of the BPaL regimen and its toxicity. Just how much LZD contributes to the BPaL regimen compared to the other constituents, and any synergic effect of the three drugs, remains to be elucidated. Despite the higher efficacy of BPaL, its wider dissemination is hampered by the high cost of LZD, monitoring requirements and morbidity. The ZeNiX trial looking at lower doses and periodic use of LZD may mitigate some of the adverse effects, moreover therapeutic drug monitoring and minimal inhibitory concentration data may allow for a lower, better-tolerated but still effective, dosing schedule.[13–15] Also, as mentioned by Oelofse et al.[5] the beneficial roles of individual drugs such as

Article submitted 9 March 2021. Final version accepted 10 March 2021.

pretomanid in decreasing contagiousness, is important when building or studying different treatment regimens. A shorter time to culture conversion might be used as a surrogate outcome parameter for this.[16] These new treatment regimens, especially when including the new drugs like BDQ and pretomanid, should also be studied or described in a cohort of children.[17]

Overall, we hope that new treatment regimens will improve outcomes.[18] Therefore, more studies and funding are needed – ideally based on adaptive trial design, in which less successful arms can be discontinued in favour of more successful arms. For future comparisons between such studies, trial designs should include standardized sampling times for culture, standardized follow-up time and ideally also PK for a subgroup. Finally, the individual role of drugs should not be forgotten, the next step will be to find a more active and less toxic oxazolidinone as an alternative to LZD.

O. W. Akkerman[1,2]
S. Tiberi[3,4]
J-W. Alffenaar[5,6,7]

[1]University Medical Center Groningen, Department of Pulmonary Diseases and Tuberculosis, University of Groningen, Groningen,
[2]Tuberculosis Center Beatrixoord, University Medical Center Groningen, University of Groningen, Haren, The Netherlands;
[3]Department of Infection, Barts Health NHS Trust, London,
[4]Blizard Institute, Queen Mary University of London, London, UK;
[5]University of Sydney, Faculty of Medicine and Health, School of Pharmacy, Sydney, NSW,
[6]Westmead Hospital, Sydney, NSW,
[7]Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Sydney, NSW, Australia
Correspondence to: Onno W Akkerman, Department of Pulmonary Diseases and Tuberculosis, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ, Groningen, The Netherlands. email: o.w.akkerman@umcg.nl

References

1 World Health Organization. Global TB report, 2020. Geneva, Switzerland: WHO, 2020. https://www.who.int/tb/publications/global_report 2020
2 Marais B, Zumla A. Advancing global tuberculosis control after the UNGA-HLM. Lancet 2018; 392(10153): 1096–1097.
3 World Health Organization. UN General Assembly High-Level Meeting on Ending TB. Geneva, Switzerland: WHO, 2018. https://www.who.int/tb/features_archive/UNGA_HLM_ending_TB/en/ Accessed April 2021.
4 van Altena R, et al. Highly successful treatment outcome of multidrug-resistant tuberculosis in the Netherlands, 2000–2009. Int J Tuberc Lung Dis 2015; 19: 406–412.
5 Oelofse S, et al. Pretomanid with bedaquiline and linezolid for drug-resistant TB: a comparison of prospective cohorts. Int J Tuberc Lung Dis 2021; 25:453–460.
6 Padayatchi N, et al. Treatment outcomes in patients with drug-resistant TB-HIV co-infection treated with bedaquiline and linezolid. Int J Tuberc Lung Dis 2020; 24: 1024–1031.
7 Conradie F, et al.; Nix-TB Trial Team. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med 2020; 382(10): 893–902.
8 Olayanju O, et al. Long-term bedaquiline-related 305 treatment outcomes in patients with extensively drug-resistant tuberculosis from South Africa. Eur Respir J 2018; 51(5): 1800544.
9 Borisov S, et al. Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report. Eur Respir J 2019; 54(6): 1901522.
10 Ndjeka N, et al. Implementing novel regimens for drug-resistant TB in South Africa: what can the world learn? Int J Tuberc Lung Dis 2020; 24: 1073–1080.
11 Alffenaar J-WC, et al. Integrating pharmacokinetics and pharmacodynamics in operational research to end tuberculosis. Clin Infect Dis 2020; 70(8): 1774–1780.
12 Zhu H, et al. Therapeutic drug monitoring of cycloserine and linezolid during anti-tuberculosis treatment in Beijing, China. Int J Tuberc Lung Dis 2018; 22: 931–936.
13 Bolhuis MS, et al. Treatment of multidrug-resistant tuberculosis using therapeutic drug monitoring. Eur Respir J 2019; 54(6): 1900580.
14 Mikiashvili L, et al. Linezolid use for drug-resistant tuberculosis in Georgia: a retrospective cohort study. Int J Tuberc Lung Dis 2020; 24: 436–443.
15 Butov D, et al. Multidrug-resistant tuberculosis in the Kharkiv Region, Ukraine. Int J Tuberc Lung Dis 2020; 24: 485–491.
16 Tweed CD, et al. Bedaquiline, moxifloxacin, pretomanid, and pyrazinamide during the first 8 weeks of treatment of patients with drug-susceptible or drug-resistant pulmonary tuberculosis: a multicentre, open-label, partially randomised, phase 2b trial. Lancet Respir Med 2019; 7(12): 1048–1058.
17 Garcia-Prats AJ, et al. Current status of pharmacokinetic and safety studies of multidrug-resistant tuberculosis treatment in children. Int J Tuberc Lung Dis 2018; 22: 15–23.
18 Furin J, Akkerman OW. Hope rises out of despair: bedaquiline and linezolid for the treatment of drug-resistant TB. Int J Tuberc Lung Dis 2020; 24: 987–988.