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EDITORIAL

Building the evidence base for shortened MDR-TB treatment regimens

IN 2007, AT THE REQUEST of the International Union Against Tuberculosis and Lung Disease (The Union), the World Health Organization (WHO) conducted an external review of a Damien Foundation pilot project in Bangladesh which was treating multidrug-resistant tuberculosis (MDR-TB) patients with a markedly shortened regimen and reporting impressive treatment success rates of approximately 85%.[1] The external review concluded that, prior to widespread implementation, additional data were needed, ideally from a properly conducted clinical trial.

In 2012, The Union, together with the UK Medical Research Council's Clinical Trials Unit and other key partners, and with support from the United States Agency for International Development (USAID), initiated the 'Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multidrug-resistant tuberculosis' (STREAM) clinical trial comparing a 9-month moxifloxacin-based regimen with the WHO-recommended 20–24 month regimen.[2] Preliminary results released in October 2017 demonstrated a favourable outcome rate of 78% using the shortened regimen despite an extended follow-up period and a rigorous definition of unfavourable outcomes.[3] Final results, not expected to change materially, are anticipated in June 2018.

In this issue of the *Journal*, Trébucq and colleagues report on the largest cohort to date to evaluate a similar 9-month regimen in nine African countries.[4] Despite the inclusion of human immunodeficiency virus (HIV) positive patients (who were minimally represented in the Bangladesh project), the treatment success rate was greater than 81%, providing additional reassurance on the generalisability of the regimen.

However, several important questions remain. First, a high proportion of deaths (19%) among HIV co-infected patients is of concern. It will be critical to explore interventions that could reduce the mortality in this vulnerable population. Second, the dosage of moxifloxacin used in this cohort study was 400 mg, rather than a higher, weight-adjusted dose used in the STREAM trial. The frequency of treatment failure for both high-level and low-level fluoroquinolone resistance, and acquisition of resistance to fluoroquinolones, were higher than reported from Bangladesh, where high-dose gatifloxacin was utilised. A better understanding of the optimal fluoroquinolone and dosage is urgently needed.[5] Third, the WHO highlighted the role of resistance to drugs included in the shortened regimen (e.g., pyrazinamide) as a determining factor in its use.[6] Trébucq et al. reported that resistance to pyrazinamide, ethambutol or prothionamide was not found to be independently associated with treatment outcomes in this cohort. Unfortunately, the proportion of patients with drug susceptibility testing results against these drugs was relatively low, precluding the ability to draw firm conclusions on this issue. Finally, the number of patients with QTcF of more than 500 ms was very small. However, electrocardiograms were performed only before inclusion and one week after initiation of treatment, unless otherwise indicated. Thus, the frequency of QT prolongation was likely underdetected. Minimum monitoring requirements for the shortened regimen in programme settings need further clarification. Timely answers to these priority questions will ensure the widest reach of a safe and effective MDR-TB treatment regimen for those most in need.

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References

1 Aung K J M, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis 2014; 18: 1180–1187.
2 Nunn A J, Rusen I D, Van Deun A, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multidrug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials 2014; 15: 353.
3 Akkermans R. 48th Union World Conference on Lung Health. Lancet Respir Med 2017; 5: 926–927.
4 Trébucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. Int J Tuberc Lung Dis 2018; 22: 17–25.
5 Van Deun A. Chiang C-Y. Shortened MDR-TB regimens overcome low-level fluoroquinolone resistance. Eur Respir J 2017; 49: 1700223.
6 World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. October 2016 revision. WHO/HTM/TB/2016.04. Geneva, Switzerland: WHO, 2016.