Improving treatment of multidrug-resistant tuberculosis: Results of the endTB randomised clinical trial

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Introduction

Tuberculosis (TB) is a major public health challenge encountered across many Médecins Sans Frontières (MSF) fields. Management of drug-resistant TB is an operational priority for MSF. endTB is an MSF-sponsored randomised trial funded by Unitaid as part of the larger endTB project. The trial objective was to examine five new all-oral, shortened regimens for patients with fluoroquinolone-susceptible, rifampicin-resistant/multidrug-resistant TB (RR/MDR-TB).

Methods

endTB was a phase 3, randomised, controlled, non-inferiority trial performed in seven countries (Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, and South Africa) in five WHO regions. Participants with RR/MDR-TB (aged ≥15 years old) were randomly assigned to six regimen groups (1:1:1:1:1:1; 9BLMZ, 9BCLLfxZ, 9BDLLfxZ, 9DCLLfxZ, 9DCMZ, or control) using Bayesian response-adapted randomisation. Experimental regimens were 9 months long; all contained 4–5 drugs, including pyrazinamide, a fluoroquinolone, either bedaquiline and/or delamanid, and linezolid and/or clofazimine. The internal, concurrent control regimen was the evolving WHO-recommended standard. Primary outcome was the proportion of favourable outcome at week 73, defined by two negative sputum culture results. The non-inferiority margin was 12%. We performed efficacy comparisons in the modified intention-to-treat population (mITT), which included all randomised participants who took at least one dose of study treatment (safety population) and who had a positive pre-randomisation TB culture, and in the per-protocol population (PP), defined as mITT excluding participants who did not receive the protocol-defined treatment. We performed safety comparisons on the safety population. This study is registered on ClinicalTrials.gov (NCT02754765).

Ethics

The endTB trial has been approved by MSF Ethics Review Board and by ethic committees of partner organisation (Harvard Medical School, Interactive Research and Development, Institute of Tropical Medicine) and each participating country.

Results

Of 754 participants enrolled between 2017 and 2021, 696 and 559 were included in the mITT and PP analyses, respectively. Median age was 32.0 years (IQR 23.0–44.0), and 264 (38%) of 696 participants were female. Overall, regimens 9BLLfxCZ, 9BLMZ, and 9BDLLfxZ achieved non-inferiority in mITT and PP analyses. 9BLLfxCZ also achieved superiority. 9DCMZ regimen achieved non-inferiority in mITT, but not in PP. 9DCLLfxZ did not achieve non-inferiority. The proportion of participants experiencing grade 3 or higher adverse events or serious adverse events was similar between the regimens. Grade 3 or higher hepatotoxicity occurred in 12.6% (78/619) of participants in the experimental regimens overall and in 7.1% (9/126) of participants in the control group.

Conclusion

The endTB trial results increase patient-centred treatment options for RR/MDR-TB with three shortened, all-oral, non-inferior regimens to a current well-performing standard of care. A fourth regimen could be considered for patients for whom bedaquiline and/or linezolid is not available. These results could be extrapolated to children and pregnant women. The implications on the MSF TB field activities are important and could lead to improved access to care and better treatment outcome.

Conflicts of interest

All authors declare no competing interests.