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Editorial

Are We Moving Towards Development of Universal Drug Regimen for Treatment of Tuberculosis?

Tuberculosis (TB) is considered to be a major global health problem and an important cause of morbidity and mortality in high burden countries including India. There were an estimated 10 million TB cases with 1.5 million deaths worldwide in 2018.[1] Around 4000 people die and 30,000 people fall ill every day. There were an estimated 2.7 million TB cases in India with 0.45 million deaths in 2018.[1] Rifampin (R), isoniazid (H), ethambutol (E), pyrazinamide (Z) in combination, remains the mainstay of the treatment for the drug sensitive TB (DS-TB) with a success rate of 85%.[1] The concept of drug-resistant TB (DR-TB) has come into existence by the development of acquired and also transmitted resistance, creating important forms — rifampicin-resistant-TB (RR-TB), multidrug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB). 3.4% of newly diagnosed and 18% of previously treated TB cases worldwide had MDR-TB in 2018. In India, 2.8% of newly diagnosed and 14% of previously treated TB cases estimated to have MDR-TB. Multidrug and rifampicin resistant TB (MDR-RR-TB) and XDR-TB are now posing a potential threat to the control of TB.[1] The World Health Organization (WHO) 'END-TB Strategy' has set targets for eliminating TB with 80% and 90% reduction in incident rate as well as 90% and 95% reduction in mortality rate by 2030 and 2035, respectively.[1,2] The Government of India intends to end TB by 2025 which is a well appreciated initiative.[3] The first step is to stop emergence of new drug resistant cases. WHO has introduced universal drug susceptibility testing (DST) in order to detect drug resistance rapidly at the time of diagnosis by using genotypic tests, such as cartridge based nucleic acid amplification test (CBNAAT) for rifampicin resistance and also line probe assays (LiPA) to detect MDR-/XDR-TB.[4,5] Another issue is that global treatment outcome of MDR-/RR-TB cases remains sub-optimal. Out of 484,000 cases of MDR-/RR-TB worldwide, 186,772 (38.6%) cases were notifiedand only 156,071 (32.2%) were enrolled on treatment with second-line drugs with treatment outcome of only 56% in 2018.[1] Out of 130,000 MDR-/RR-TB cases in India, 58,347 (45%) were notified and 46,569 (36%) were enrolled on treatment with second-line drugs with treatment success rate of only 48%.[1] All these drug resistant cases are usually treated with longer regimens containing a combination of second-line drugs including injectables for duration of at least 18-24 months.[4] The reasons for sub-optimal outcome are possibly due to lengthy, expensive and toxic second-line drugs particularly injectables leading to poor compliance. WHO has recently recommended treatment of MDR-/RR-TB patients with 18-20 months all oral longer regimen containing newer and repurposed drugs for improving outcome.[5] Shorter treatment regimen was also introduced with duration of 9-12 months for MDR-/RR-TB with an aim to reduce the cost and duration of the treatment, thereby, improving the compliance and outcome.[4-6] It is indicated in subset of MDR-/RR-TB patients who either have not been previously exposed to second-line drugs or no documented resistance to fluoroquinolones and second-line injectable agents at baseline. Shorter regimen reported to have statistically-significant higher likelihood of treatment success than those received longer conventional regimens (83% *versus* 56%).[6] A phase 3 randomised control trial (RCT) STREAM (Standard Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB) Stage-1 also reported that a shorter regimen was non-inferior with respect to primary efficacy outcome (78.8% *versus* 79.8%) and was similar to the longer regimen in terms of safety in patients with MDR-/RR-TB.[7,8] However, there are various shortcomings associated even with approved shorter regimen. The shorter regimen still requires a minimum four months of treatment in an intensive phase with drugs having poor toxicity profile and logistical challenges of multiple intramuscular administration of injectable aminoglycosides leading to poor adherence. Another important issue is that evidence remains weak regarding efficacy of shorter MDR-/RR-TB regimens in all settings or population and especially outside trial conditions with respect to DST pattern, human immunodeficiency virus (HIV) status, extra-pulmonary involvement and pregnancy. A study from Mumbai reported that <5% of MDR-TB patients were eligible for empiric shorter regimen after screening with clinical characteristics and DST.[9] A second stage of STREAM 2 trial is ongoing to test two additional shortened treatment regimens using bedaquiline.[7] This extended study is evaluating a nine months all oral regimen without injections avoiding toxicity and an even shorter simplified six months regimen.

Various trials are ongoing to design innovative shorter regimens containing newer and re-purposed drugs that can serve the purpose to treat drug sensitive (DS)-TB in addition to DR-TB cases favouring a universal treatment approach. These trials are conducted by Research Excellence to Stop Tuberculosis resistance (RESIST-TB), an initiative adopted under 'END-TB Strategy' by WHO to promote and conduct research on therapy for rapid control of DR-TB.[10] The regimens carry potential advantages such as reduced drug burden, shorter duration, shorter culture conversion time, efficacy and all oral route of administration with better toxicity profile. Pretomanid (Pa) is one of the promising

newer drug that has shown to increase treatment success in MDR-/XDR-TB and can be considered as backbone of universal drug regimens.[11] Pretomanid has a distinct mechanism of action from other anti-TB drugs and is unaffected by the bacterial mutations that confer resistance to other TB drugs, so it is equally effective against DR-TB and also DS-TB.[11] The Nix-TB trial is a single-arm, open-label trial reported cure rate of 90% (MDR-TB–92%; XDR-TB–89%) after 6-7 months of treatment with regimen containing Bdq, Pa, and linezolid (Lzd).[12] A Phase-2A, partially double-blind, randomised trial reported significantly higher bactericidal activity after two weeks with regimen containing Pa, moxifloxacin (Mfx) and pyrazinamide (Z) than that for other regimens containing Bdq alone, Bdq and Z, Bdq and Pabutnot for Pa and Z, and comparable with that of standard treatment HRZE (isoniazid, rifampicin, pyrazinamide and ethambutol).[13] A multi-centric, open-label partially randomised Phase-2B trial observed that Pa containing groups showed significantly higher bactericidal activity against DS-TB treated with regimens (Mfx, Pa-200 mg, Z) and (Mfx, Pa-100 mg, Z) as compared to standard HRZE group.[14] The same regimen showed better bactericidal activity among DR-TB patients. Another multi-centric, open-label partially randomised Phase-2B trial reported that Pa containing groups in combination with the daily dose or loading dose of Bdq and Z showed significantly higher bactericidal activity against DS-TB for the groups as compared to HRZE group.[15] Regimen containing Pa, Bdq, Mfx and Z showed better bactericidal activity among DR-TB patients irrespective of HIV status. The Pa containing regimens were also associated with poor safety profile than the HRZE group (9% *versus* 3%) for people with DS-TB. Several limitations were associated with these trials, such as shorter duration (8 weeks) for assessing bactericidal activity, non-placebo controlled or blinded and possibility of bias due to involvement of the sponsorship in methodology and data analysis.

Merits of universal regimens include shorter treatment duration as well as culture conversion time leading to decreased risk of transmission of infection among all forms of TB patients including HIV co-infection and enhancement of streamlined care delivery.[16] Various demerits have also been postulated, such as rapid amplification of acquired resistance to effective newer drugs due to strain variation or selection of drug resistant strains, pharmacokinetic variability and de-prioritisation for precise diagnostic tests and newer drugs due to decrease demand for DST.[17] Other demerits include more challenging management of drug resistance and toxicity, lack of reserve regimens or drugs, vigorous efforts to maintain drug stocks by ensuring regular supply and scaling up productivity, deviation from the patient centric and sub-optimal dosing in pediatric cases. However, use of novel universal drug regimens should not be deferred despite of these uncertainties. These regimens have potential to reduce transmission of drug resistance and should not be compromised for fear of development of resistance in DS-TB cases. The newer drugs can still be continued despite of documented resistance. This requires support of strong and rapid drug resistance surveillance.

An important issue remains whether these upcoming shorter regimens will work in all settings, and especially, outside trial conditions needs extensive research. It has been projected that the universal approach will remain only for limited duration due to probability of gradual development of acquired resistance (5-10 years) to newer drugs like Bdq (Dlm) or Pa.[18] Most of the regimens are currently in Phase 2A/2B trials and require to undergo Phase-3 trials for further validation. Given the significant burden of TB worldwide coupled with unfavourable outcomes, it is vital to evaluate these novel universal regimens under programmatic conditions. It is possible that universal regimen might help for elimination of TB early.

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