Editorial

Drug-resistant tuberculosis: Progress towards shorter and safer regimens

Drug-resistant tuberculosis (DR-TB) continues to be a global health crisis. In 2017, an estimated 558 000 people had rifampicin-resistant TB (RR-TB), and 82% of them had multidrug-resistant TB (MDR-TB); 3.5% of new TB cases and 18% of previously treated cases had MDR/RR-TB. A quarter of the DR-TB cases globally were from India.[1] Only about 25% of these estimated MDR-TB or RR-TB were diagnosed and notified. The remainder were either missing or were on ineffective first-line treatment for the need of drug-susceptibility testing (DST).

To tackle this problem, several countries are scaling up the capacity for universal DST and also introducing newer drugs (e.g. bedaquiline) as well as shorter, individualized regimens, based on DST results.[2]

In a study published in this issue of *Lung India*, Singh *et al*. reported on the treatment outcomes of a modified DOTS-plus strategy among 98 consecutive culture-proven adult MDR-TB patients from June 2009 to February 2010 in a single center in North India.[3] Patients were excluded if they had taken second-line drugs for more than 1 month, were pregnant, or had concurrent major medical or psychiatric illness.

The modified DOTS-plus strategy consisted of six drugs (KM, OFX or LFX, ETO, CS, PZA, and EMB) in the intensive phase (IP), followed by four drugs (OFX, ETO, CS, and EMB) in the continuation phase (CP). Treatment included monthly follow-up with clinical, radiological, and bacteriological assessment (sputum smear advised monthly till conversion then quarterly; culture for *Mycobacterium tuberculosis* at 0, 4, 6, 12, 18, and 24 months). The duration of IP ranged from 6 to 9 months depending on culture results at the 4th month of treatment and CP for a minimum of 18 months. Drugs were provided free of cost, and regular supply of medicines and laboratory supply were ensured by a dedicated team of clinicians, microbiologists, and a laboratory technician. Patient and family members were counseled, and adherence to medication and adverse events (AEs) were monitored.

The MDR-TB cohort had a fairly extensive disease with 95% having bilateral lung involvement. The mean duration of total illness was 4.8 ± 3.6 years, and the duration of anti-TB treatment received by the cohort before referral was 26 ± 12.3 months. The cohort was resistant to a mean of 3.17 ± 1.06 drugs. With the health education, intensive adherence counseling, AE surveillance, and the drug treatment as in the protocol, the sputum smear and culture conversion rates were 75/81 (92.5%) and 71/81 (87.7%), respectively. 81 (82.7%) of patients completed the treatment, with 71 (74.5%) declared successfully cured, 10.2% failed, 7.1% defaulted, and 10.2% expired.

The rate of success in the present study was fairly high, compared to global averages for DR-TB. However, the study excluded 21/132 (15.9%) patients as 8 (6.1%) were exposed to SLDs >1 month and 13 (9.8%) showed non-MDR resistance patterns. This group could have had poor outcomes had they received the standardized regimen. Patients with poor outcomes in the present study were likely to be drug addicts, likely to have >2 previous episodes of TB, and likely to have resistance to both KM and OFX. This highlights the critical need for universal DST, including second-line DST and appropriate treatment based on DST results.

In an individual patient data meta-analysis of 12,030 pulmonary MDR-TB patients, from 25 countries in 50 studies, 7346 (61%) had treatment success, 1017 (8%) had failure or relapse, and 1729 (14%) died.[4] Compared with failure or relapse, treatment success was positively associated with the use of linezolid, levofloxacin, carbapenems, moxifloxacin, bedaquiline, and clofazimine. There was a significant association between reduced mortality and use of linezolid, levofloxacin, moxifloxacin, or bedaquiline. Compared with regimens without any injectable drug, amikacin provided modest benefits, but kanamycin and capreomycin were associated with worse outcomes.

In the present study, AEs were reported in 46 (46.9%) patients; major AEs were reported in 17.4% of patients, with the most common being deafness induced by KM and psychosis by CS. The limitation of the present study is its small sample size and absence of PLHIV among the MDR cohort who are known to have poor outcomes. In addition, this study was performed about a decade ago, and since then, Indian and global guidelines have evolved, and new drugs and regimens have emerged.

In 2010, the Revised National Tuberculosis Control Programme (RNTCP) guidelines for the Programmatic Management of Drug-Resistant Tuberculosis in India were published[5] and updated in 2017.[6] In 2014, the standards for TB care in India were released, comprising 26 standards, with standard 9 specifically addressing the treatment of drug-resistant TB in India.[7]

Based on the WHO recommendations, India adopted in 2017 a shorter MDR-TB regimen lasting 9–12 months for MDR/RR-TB who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, which is a standardized regimen, with 4–6 Am-Mfx-Pto (Eto)-Cfz-Z-Hhigh-dose-E/5 Mfx-Cfz-Z-E. India also adopted universal DST for all diagnosed TB patients, when offering an upfront CBNAAT (i.e. Xpert MTB/RIF) to all presumptive TB patients among key populations and incorporated monitoring and management of adverse drug reactions. In March 2017, the RNTCP published a new National Strategic Plan for TB Elimination 2017–2025.[8]

The global guidelines have also advanced in the past few years. In 2019, the WHO published their updated, consolidated guidelines on DR-TB, recommending several major changes.[9] Drugs have been regrouped into three categories and ranked based on the latest evidence about the balance of effectiveness to safety.[4]

Group A are the drugs to be prioritized, namely levofloxacin/moxifloxacin, bedaquiline, and linezolid.[10] Group B are the drugs to be added next, namely clofazimine, cycloserine/terizidone, and Group C which include delamanid are the medicines to be included to complete the regimens and when agents from Groups A and B cannot be used. Drugs no longer recommended are injectables such as kanamycin and capreomycin, given increased risk of toxicity, treatment failure, and relapse associated with their use in longer MDR-TB regimens.

Bedaquiline and delamanid are the newer drugs for the treatment of DR-TB. This year, the US Food and Drug Administration is expected to approve another new drug called Pretomanid.[11] A short course, all-oral treatment of MDR-TB is the major goal today. The Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis 1 study has shown that high-dose moxifloxacin containing short-course regimen was noninferior to a long regimen with respect to the primary efficacy outcome and safety.[12] Other trials are evaluating short-course regimens with bedaquiline against the WHO-recommended regimen.[13] The Nix-TB trial with BPaL regimen (bedaquiline, pretomanid, and linezolid) for XDR-TB has shown very promising results with favorable outcomes in 90% of patients after 6 months of treatment and 6 months of posttreatment follow-up.[11]

The Treatment Shortening of MDR-TB Using Existing and New Drugs Trial is underway to evaluate the effectiveness and safety of a new shorter regimen comprising four oral drugs, including delamanid, linezolid, levofloxacin, and pyrazinamide, for the treatment of fluoroquinolone-sensitive MDR-TB.[14]

The results from these trials provide evidence for adopting a shorter, safer, and more convenient treatment regimen for DR-TB. To support the uptake and scale-up of such shorter regimens, it is paramount that providers and national programs are guided by phenotypic and/or genotypic DST to offer individualized regimens.[2] The scale-up of diagnostics such as CB-NAAT and line probe assays has made DST easier, and technologies such as sequencing are becoming easier and more affordable every passing year. The future of DR-TB treatment heavily relies on our ability to exploit novel DST tools, new drug regimens, and digital adherence support tools. India has a chance to lead from the front in this arena.

Kavitha Saravu[1,2], Madhukar Pai[2,3]

[1]Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India, [2]Manipal McGill Program for Infectious Diseases, Manipal Center for Infectious Diseases,Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, Karnataka, India, [3]McGill International Tuberculosis Centre, McGill University, Montreal, Canada

E-mail: kavithasaravu@gmail.com, kavitha.saravu@manipal.edu

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