The changing trends in MDR-TB management

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This editorial may be cited as: Basit A, Javaid A, Ghafoor A. The changing trends in MDR-TB management. Pak J Chest Med 2021; 27(02): 53-54

TB remains among the top 10 causes of death globally. Given drug-resistant tuberculosis (Dr-TB) becoming a public health crisis, the diagnostic, prevention and management guidelines have been revisited.[1]

The last decade was about WHO developing and issuing evidence-based policy recommendations on managing and caring for patients with drug-resistant tuberculosis.

Several new medications and regimens have lately been brought together to control the DR-TB epidemic, along with various diagnostic tools and preventative strategies. These are novel (bedaquiline- and delamanid) preparations or shorter and customized treatment regimens and re-purposed (linezolid and clofazimine) preparations. At the same time, older drugs, such as injectables, ethionamide, and para-aminosalicylic acid, have been relegated due to meagre effectiveness and severe side-effect profiles.

The earlier long term regimen (LTR) of a 2-year standardized regimen including second-line injectables (SLI) is now replaced by a shorter treatment regimen (STR) for Fluoroquinolone (FQ) sensitive patients and LTR 1, LTR 2 and LTR 3, depending on past drug history and results of drug susceptibility testing. Injectable agents are no longer a requirement as primacy medications for MDR-TB treatment regimens, and entirely oral regimens have been endorsed as a choice.[3]

Since the beginning of 2010, when NTP began controlling DR-TB through programmatic management (DR-TB (PMDT), a two-year LTR was used for RR/MDR-TB. In 2018, the STR lasting 9-11 months gradually replaced the LTR in patients without FQ resistance. All oral LTR was initiated in July 2019 following WHO recommendations. Since February 2020, the injectable drug in STR was replaced by bedaquiline (Bdq) in line with new WHO guidelines 2019 and June 2020.[2,3]

The treatment success rate declined as the case number increased to above 60%, with deaths and loss to follow-up (LTFU) remaining the main reasons for unfavourable outcomes. However, it appears to have improved in 2017 and 2018. As among RR patients enrolled, the first half of 2018 treatment success was 65%. When assessed by regimen and resistance to FQ, patients on STR (with injection, mainly FQ-Sensitive) had the highest success rate (72%) but with high LTFU and deaths, indicating that shortening the regimen improved outcome did not prevent deaths and LTFU. LTR in FQ-Sensitive with comparable patients as STR had a slightly lower success rate (68%) and a higher failure rate (5%). LTR FQ-Resistant had a lower success rate (60%), high death rate and very high failure (11%). LTR FQ-Unknown had the lowest success rate (57%), with a high death rate, LTFU, suggesting that not having a test for FQ-resistance (LPA) may be a proxy for other unfavourable factors.

WHO has placed medicines of DR-TB into three groups (A, B and C). Group A consists of Newer fluoroquinolones Moxofloxacine and Levofloxacin (Mfx and Lfx), Bedaquilline, Linezolid; Clofazimine, Cycloserine, Terizidone are in Group B while Group C comprises Pyrazinamide, Delamanid, Ethambutol, Imipenem, Ethionamide, Amikacin and PAS.

In Pakistan, the National TB Control Programme (NTP) has developed three standardized LTR regimens to facilitate implementation, depending on FQ resistance and previous use of SLD. NTP suggests that entirely oral regimens should be the preferred option, and injectable agents are no longer considered as the medicines on priority. However, SLI

is still included in the LTR for FQ-resistant patients in Pakistan, as there are concerns that removing SLI increases the risk of acquired resistance to Bdq 5. Treatment may be started with five agents to evade the necessity of replacing a medicine after it has been started. The total duration for DR-TB treatment is 18-20 months which may be altered, conferring to the patient's response to treatment. In injectable regimens, the intensive phase is 6 months with a total treatment duration of 18 months and 16 months after culture conversion. The treatment post culture transformation period may be improved according to the patient's response post-therapy and risk factors for relapse or management failure.

Patients not eligible for STR are started on one of the three LTR regimens. In patients who have not used SLDs in the past are started on LTR1 when FQ sensitive or still unknown, LTR2 if any FQ resistance, while LTR3 is recommended for patients with either failure of STR/LTR, or relapse of STR/ LTR or the patient has resistance to FQ as well as Bdq/SLI.

Rifampicin Resistant (RR) patients can also be treated with other short regimens in projects under strict operational research (OR) conditions. These regimens include Modified STR all-oral regimens (many using Lzd) and the BPal regimen using Bdq, Pretomanid and Lzd and for six months in patients with FQ resistant strains. Other OR options can also be explored as and when required.

To conclude this discussion, it has to be understood that to improve outcomes at the district level, in addition to the more effective regimens, decentralization must be interlinked and closely coordinated with main PMDT sites.[6] It is crucial to understand that the fate of the treatment also depends significantly on the available psychosocial support and speedy molecular diagnostic tools like LPA. There is a dire need for intensified research and development in terms of evidence-based research, scientific breakthroughs to decline TB incidence rate, and improved management to achieve Sustainable Development Goals (SDG) and 2030 targets set via the End TB Strategy. It is suggested both by WHO and NTP that MDR-TB management can be further improved using shorter and better regimens, closing gaps in TB diagnosis, patient-centred support for medication adherence and active TB drug safety monitoring and management (aDSM).[7] NTP must choose between adhering to the obsolete treatments or adopting new, shorter all-oral regimens that are expected to be more effective and safe. It is already evident with data support that implementing the new regimens under-functioning research settings, NTP will bring benefits to local patients and help to generate substantial evidence that will benefit other patients across the region.

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