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Boon of the BPal Regime: Bane for Multi Drug Resistant Tuberculosis in India

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ABSTRACT

A novel regime for treatment of MDR TB has been launched consisting of BDQ, PRT and LNZ. Immense potential lies in its short term (6 months), efficacious drugs and lesser adverse events. A very good cure rate of around 90% have been achieved in Clinical trials including one from India. A contingent as well as circumspect roll out of the regime in all parts of India may be momentous for MDR TB control and TB elimination.

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India has the maximum number of Tuberculosis (TB) patients, maximum number of Multi-Drug Resistant (MDR) TB patients and maximum number of deaths attributable to TB in the world [1]. National TB Eradication Program (NTEP) is an extremely ambitious country wide strategy to achieve TB elimination in India by 2025 [2]. The NTEP has made significant improvement in the management and outcomes of Drug Sensitive (DS) TB in India [3]. This step is a momentous indicator towards a nation wise commitment in the elimination of the menace of this deadly disease However, MDR TB in India is increasing, thereby posing a threat to the overall success of NTEP [4].

The reasons for the increase of MDR TB are multifactorial. Inappropriate treatment regimes, lack of developed country wide laboratory infrastructure, interrupted supply of drugs, non-compliance with treatment especially due to adverse events etc. are some of the reasons for increased MDR TB cases. Currently, the number of cases is also increasing due to enhanced transmission to contacts of MDR TB patients as the number of such patients has increased considerably. There is country wide effort to curb this problem but due to the size of our country and its large population, it may take some time for effective development of laboratory infrastructure for quick and reliable diagnosis and an uninterrupted supply of efficacious drugs for effective treatment in these patients [5].

The second line drugs which are currently used for treatment of MDR TB are less efficacious and more toxic and the treatment regime may be as long as 18–20 months leading to non-compliance by the patients with resulting treatment failure. However, there is renewed hope in the management of these patients in the form of novel drugs with good therapeutic potential against Mycobacterium Tuberculosis (MTB), the causative agent of TB. Bedaquiline (BDQ), Delamanid (DLM) and Pretomanid (PRT) are comparatively newly discovered anti-tubercular agents which hold immense potential in combatting MDR-TB, with high efficacy and lower risk of side effects [6-8].

MDR TB by definition means resistance to at least Isoniazid (H) and Rifampicin (R), the major first line drugs for anti-tubercular treatment (ATT). R-Resistant(R) TB is determined by an automated test which identifies MTB with R resistance simultaneously, namely the Cartridge-Based Nucleic Acid Amplification test (CBNAAT) within 2 hours. Its sensitivity and specificity are very high [9]. R(R) TB is considered a proxy for MDR TB and is managed on similar lines. Pre-extensive (Pre-XDR) TB is MDR TB with additional resistance to the Fluoroquinolones (FQ) such as Levofloxacin and Moxifloxacin. XDR TB is Pre-XDR TB with additional resistance to BDQ or Linezolid (LNZ), the most important drugs for MDR TB treatment.

LNZ is an antibiotic of the oxazolidinone class which has been used for treatment of numerous infections. Its efficacy against MTB is remarkable and hence it is now a major weapon to combat MDR TB [10]. BDQ belongs to a class of drugs called Diarylquinolines and is now an integral part in MDR TB regimes, being a very effective medicine against MTB. DLM and PRT both belong to the class of drugs in the nitroimidazole group having similar mechanisms of action and significant cross-resistance to each other [6-8].

One of the main factors associated with non-compliance to treatment of MDR TB is the duration of the regime. As already mentioned, most cases have to take treatment for 18-20 months (All oral longer BDQ based regime). The all-oral short course regime for MDR TB with BDQ has limited applicability and involves 9-11 months of treatment. Adverse effects of the drugs along with high pill burden also contributes to patients stopping treatment in between, thereby compromising the final outcome. The long duration of treatment also puts extra burden on the healthcare and laboratory resources along with drug supplies [5].

In spite of some disappointment in our goals for MDR TB control in India, a new hope has arisen. A very promising treatment regime, the BPaL regime, has been formulated by the WHO after the NIX TB trial results in South Africa [11]. A recently concluded study

in India with a sample size of 403 MDR TB patients has shown success rates above 90% [12]. The regime has received a positive nod for introduction in India which is a very encouraging step for the success of NTEP [13].

The BPaL regime consists of three drugs – BDQ, PRT and LNZ given over a period of 6 months (26 weeks). The regime provides efficacious treatment along with shorter time duration. Studies have shown good outcomes with the regime and WHO has stated that BPaL may be used programmatically for patients with R(R) TB who are 14 years or older in age without a prior exposure to BDQ, LNZ and PRT of more than 1month [14].

One of the major issues with this regime is LNZ toxicity. Since the toxicity of LNZ is both cumulative as well as temporal, myelosuppression, irreversible loss of vision and debilitating peripheral neuropathy associated with LNZ are typically seen as the duration and overall exposure to LNZ increases [15]. The study from India has shown comparable efficacy in treatment outcomes in Pre-XDR and treatment-intolerant/nonresponsive MDR TB patients in doses of 600 mg/day of LNZ for 26 weeks as compared to dosage reduction of LNZ to 300 mg/day > 9 or > 13 weeks 600 mg/day along with PRT and BDQ in the standardised doses. This study reflects comparative results in lesser cumulative LNZ doses [12].

Addition of Moxifloxacin (Mfx) in the regime is recommended by the WHO (BPaLM). All efforts should be undertaken to determine the susceptibility of MTB to FQ but as this may not always be feasible, treatment should not be delayed. Baseline FQ resistance in MDR TB patients in India has shown to be as high as 36% to 50% [16,17]. However, documented susceptibility to FQ should prompt addition of Mfx to regime. A High dose Mfx has not been shown to improve outcomes in FQ resistance but may enhance side effects. Hence, high dose Mfx may not be used [18].

Though BPaL regime has offered a new promise in the management of MDR TB, baseline resistance to LNZ and especially BDQ has to be kept in mind because there is some evidence to support that baseline resistance to these highly potent drugs is rising [19,20]. Since DLM is already being used in India, baseline resistance to PRT can occur because of cross-resistance to DLM even though there is not complete cross-resistance between the two [21].

To conclude, India's crusade against TB especially MDR TB has received a terrific boost by the BPaL regime. However, casual and/or injudicious use may be detrimental and circumspection is required to get the maximal benefit from this valuable regime.

The Authors' declare no conflict of interests.

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