CORPUS PUBLISHERS

Global Journal of Infectious Diseases (GJID)

Volume 2 Issue 1, 2022

Article Information

Received date: Sep 15, 2022

Published date: Sep 27, 2022

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Keyword

Tuberculosis; MDR, Bedaquiline; Short-Course; Fluoroquinolone; Baseline; Failure; Amplification; XDR.

Mini Review

Bedaquiline-Based Short Course Regime for MDR-TB -"The Indian Scenario"

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Abstract

India ranks highest in number of Tuberculosis (TB) and Multi Drug Resistant (MDR) TB patients globally (World Health Organization. Global tuberculosis report (2018). Maximum number of deaths due to TB also occur in India. A short course regime for treating Fluroquinolone (FQ) Sensitive MDR TB has been recommended by the World Health Organization (WHO) in 2020 with a duration of 9-11 months. India has also adopted the BDQ Short course regime for MDR-TB patients with multiple exclusion criteria. The excluded patients would receive a longer BDQ based regime which may last 18-20 months. The purpose of this mini-review is to emphasize the possibilities of high failure rates in the BDQ based short course regime, especially in the Context of India due to high baseline FQ resistance and an acute shortage of Drug Sensitivity Tests (DST) tests especially for FQ. Moreover, the need of High dose Isoniazid (H^h) in the regime may be only a toxic addition in about 80% of patients leading to adverse effects, some of which may be fatal. Failure of BDQ-based short course regime would lead to a catastrophic amplification of the resistance of critically essential drugs such as BDQ and Clofazimine (CFZ). Chances of cure in such patients with Extensively Drug Resistant (XDR) TB would be slim, if not altogether absent.

Introduction

Tuberculosis (TB), the disease caused by Mycobacterium Tuberculosis, is a major infectious cause of morbidity and mortality in developing countries, including India. India has maximum number of TB patients and also the largest number of Multi-Drug Resistant (MDR) TB patients [1]. Maximum number of deaths due to TB in the world (around 34%) was reported in India in 2021 [2]. This underscores the importance of proper and complete treatment of TB in India including MDR TB. There is now a strong and dedicated political commitment under the National Tuberculosis Elimination Programme (NTEP) to eliminate TB from India by 2025.

Discussion

The WHO recommended a Bedaquiline (BDQ) based short-course regime for Fluoroquinolone (FQ) sensitive MDR-TB (resistance to at least Rifampicin and Isoniazid) in 2020 in which Second Line Injectables (SLI) have been replaced by BDQ. The decision to make FQ Drug Susceptibility Testing (DST) mandatory by WHO was considered a crucial step which eliminated any ambiguity in starting BDQ-based Short Course Regime for FQ sensitive MDR-TB [3]. The same regime has been adopted by the NTEP. The BDQ based short-course regime in India is started on the basis of Cartridge Based Nucleic Acid Amplification Test (CBNAAT) for Mycobacterium Tuberculosis which detects the bacterial DNA and simultaneous confirms or rules out Rifampicin Resistance (RR) which is used as a proxy for MDR TB, as most cases of RR TB also have Isoniazid (H) resistance in India. The Indian Regime as yet does not include a mandate of ruling out FQ resistance by a Second Line Drugs (especially FQ) Line Probe Assay Result (SL-LPA), thereby maintaining a certain ambiguity (which in its most parts is totally unavoidable) as LPA is only available in central apex TB institutes and there may be considerable delay in reports to come by which the status of FQ resistance and the mutation type (inhA, KatG) of Isoniazid (H) by First Line-LPA (FL-LPA) is known. All these points have already been covered in a previous publication of the author [4]. The Covid-19 Pandemic caused by SARS-CoV-2 which caused widespread devastation and death in India as well as other countries also has led to a tremendous stress on the Laboratory services and consumables/Kits that were used on a massive scale to diagnose and manage the deadly virus. This further caused exhaustion of laboratory services and supplies for TB related molecular tests. All stakeholders in NTEP all over the country are motivated and trying the best at their respective levels for the Goal of TB elimination but we have to reconcile ourselves to the fact that the total capacity building for FL-LPA, SL-LPA and Liquid Culture may still take considerable time to spread over the entire country.

Meanwhile, we still have to face and deal with the menace of MDR-TB, which is constantly attacking the Indian populace. The NTEP of India has defined certain exclusion criteria for BDQ-based short course regime. However, if FQ resistance is not known due to delay or unavailability of SL-LPA report, patient is initiated on the Shorter Regime (barring certain exclusion criteria) which would comprise of Ethionamide (Eto), High dose Isoniazid (H^h), High Dose Moxifloxacin (Mfx^h), Clofazimine (CFZ), Pyrazinamide (Z), Ethambutol (Eth) and Bedaquiline (Bdq-6mths) in Intensive Phase (IP), 4-6 months (others). Continuation Phase (CP) is of 5 months which includes Mfx^h, CFZ, Z and Eth for 5 months, making a total duration of 9-11 months. Follow-up is by smear

examination after 2nd month and if sputum is positive on 4th month, then culture/molecular test for SL-LPA is initiated and IP is extended by 2 months [5]. As we can see the only difference between the present and the previous short-course regime is replacement of Second-Line Injectables (SLI) with BDQ and replacing Levofloxacin with Mfx^h. A recent study has shown a baseline FQ resistance of around 32% in our country [6]. However, even this may be an underestimate because a previous study had showed baseline FQ resistance in India to be as high as almost 50% [7]. To start a BDQ based regime in which 33 to 50 % of patients are likely to be Pre-XDR TB (MDR-TB with additional resistance to FQ) requires a great deal of caution as FQ resistance can amplify the drug resistance at all levels and can wreak havoc with the drugs leading to very high levels of Extensive Drug Resistant TB (XDR-TB) which includes BDQ resistance. Mfx^h may work in about 60 to 70 % of patients with FQ resistance but even this has come under a cloud after the results of a very recent study carried out in a tertiary care centre in Mumbai have been published [8]. This study has demostrated that Mfx^h may not improve the outcome of a regime if low grade Mfx resistance is present. South Africa has also introduced a BDQ based short course regime in which they have included Linezolid (LNZ) also [9]. One may hesitate a little before including LNZ in the Indian Regime because of its adverse effect profile. However, since the toxic effects of LNZ increase temporally, thus it may be added to the regime after checking for Haemoglobin $\geq$ 8 g/dl and an eye examination. It is a humble suggestion of the author that it may be used for 600 mg once daily at least for IP (4 months) and then its dose may be reduced to 300 mg/day.

Till the end of CP (5 months). Such dose modification has been found to be successful in continuing LNZ based regime and also does not affect the outcome albeit greatly reduces the toxicity of the regime [10,11]. The BDQ based short course regime of India as per the author's humble opinion may also not include H^h as inhA mutations are present in only about 20% patients of MDR TB with H resistance [12]. Since H mutations (inhA, KatG or both) can only be known by LPA whose results may be delayed or not present due to reasons mentioned above, 80% of patients may receive a high doses of a toxic substance (H) leading to a plethora of side-effects some of which may be fatal (Psychosis, acute hepatitis, Severe Neuropathy, Seizures etc). However, the South African regime also contains H^h but it is justified in their context as inhA mutations are more common there and there is a very high rate of HIV co-infectivity which confers a high level of R mono-resistance (38%), something rarely seen in India [13].

Conclusion

To conclude, this review attempts to focus on the possibility of a successful outcome of BDQ based shorter MDR TB regime in context of India especially in the very practical and unavoidable view of shortage of Laboratory facilities for important molecular based and other tests such as FL-LPA, SL-LPA, Liquid Culture etc. and thus ensuring a more robust baseline regime with lesser toxicity. The author humbly suggests without any pretension that addition of LNZ and omission of H^h may really go a great way in making the NTEP BDQ short course regime successful. Failure in these cases would lead to BDQ resistance and thus Extensive Drug Resistant (XDR) TB. Needless to add, the patients' survival chances would become dismal and bleak and cure would become far more difficult if not totally impossible.

Conflict of Interest

None

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