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Case Series

FOLLOW-UP CASES OF BEDAQUILINE IN XDR-TB PATIENTS: A CASE SERIES

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ABSTRACT

Tuberculosis has consistently maintained its lead position in being among the top 10 causes by means of single-cause etiology for death among infectious disease patients. On top of it, now multi-drug resistant cases of tuberculosis (MDR-TB) are raising concern. The vision of tuberculosis eradication gets a major setback with a total of 206,030 million cases being reported worldwide with MDR or rifampicin-resistance MDR-TB in 2019. Bedaquilline a relative recent drug is being made available for the treatment of MDR and extensive drug resistance (XDR) TB under NTEP. It is being provided as a part of 2nd line of drug therapy. Regarding the drug's efficacy and safety profiling Bedaquiline has been under extensive clinical trials at medical institutes and hospitals of reputation at national level. The treatment options available to treat XDR-TB remain extremely limited at the cost of being less effective, expensive and with more side effects. Even after the availability of potent anti-tubercular drugs, XDR Tuberculosis is proving to be more resistant to all possible drugs available to work against it.

Keywords: Bedaquiline, XDR-TB, NTEP.

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INTRODUCTION

Worldwide, tuberculosis is one of the leading causes of death. If raked for causes of mortality due to any single infectious agent, tuberculosis is placed within 10 such causes of death rank due to single cause mortality. This is even ahead of death by Human Immunodeficiency Virus (HIV)/AIDS infection. As more than 50% of cases of tuberculosis are accounted for by the BRICS countries (that is, Brazil, Russia, India, China, and South Africa), multidrug-resistant tuberculosis (MDR-TB) remains a public health disease of extreme concern for the whole world [1]. Due to globalization, any disease cannot remain limited to any one country of its making, a glaring example of which was seen in the recent COVID crisis in the year 2020 to early parts of 2022. In the same line, MDR TB is a health-security treat for the whole world! The magnitude of the problem can be assessed from the numbers where globally 2,06,030 people were diagnosed and also notified in 2012 with MDR TB (MDR/RR-TB) [2]. This data is before the COVID crisis! In COVID times when there was a worldwide epidemic, patients of tuberculosis (also any other disease), were left with no diagnosis, no supply of medicines, no follow-up visits, or any DOTS strategy.

MDR-TB is known to be cured with support from extensive supervised chemotherapy, up to 2 years of continuous and persistent treatment and with use of a combination of various second-line drugs. The 2nd line of drugs is known to be expensive and are to be used for a longer period, making therapy of MDR-TB quite expensive to treat. Bedaquiline (BDQ) a diarylquinoline, is a new drug against mycobacteria [3] which was approved in 2012 by FDA for the therapy of MDR pulmonary tuberculosis in adults in combination with other second-line agents.

The mechanism of action is different from the current existing anti-tuberculous drug. It has its effect in blocking the proton pump in the mycobacteria. Proton pump is used by ATP synthase for the production of ATP in the mycobacterium which in turn is essential for cellular energy production [4]. Loss of cellular energy production leads to growth inhibition within hours. This is achieved by the addition of BDQ to the MDR and XDR tuberculosis regimen.

Till now, BDQ has been used in a very limited number of patients who fall within the specified criteria for its usage. Still, with this limited and watchful usage, reports of BDQ-resistance and BDQ-resistant strains have been emerging from some sites [5,6]. Presently, its known mechanism of action includes mutations within the *atp*E, *Rv0678* & *pep*Q genes. Mutations MmpL 5 efflux pump repressor generate low-level BDQ resistance and clofazimine (CFZ) cross-resistance [7]. BDQ being a very recent introduction to an anti-tuberculous drug regimen in India in the year 2016, we hereby report three BDQ-resistant cases.

Here we present three cases of XDR-TB. Before the start of the case study, written informed consent was taken from all three patients. All were on BDQ regimen but after the completion of the said regimen, within one to 2 years, patients were again found to be positive for tuberculosis. All the patients were followed up till the end.

CASE REPORT 1

A 29-year-old female weighing 40 kg, presented first with symptoms of tuberculosis in 2020. She was treated with various anti-tubercular regimens with standard doses according to Revised National Tuberculosis Control Program (RNTCP) Programmatic Management of Drug Resistance TB (PMDT) since 2016. In 2016, the patient was treated with Cat-I 2H3R3Z3E3 (INH-600mg, R-450mg, Z-1500mg, and E-1200mg) thrice a week for 2 months in a private hospital, at her in-law's house. As the patient had disputed with her husband and had come back to her maternal house, she discontinued the treatment from a private hospital and took consultation at a government tertiary care hospital. Here, a patient was put in the category for default of treatment. After a drug-sensitive test, the patient was diagnosed with MRD-TB and treated with a short-term regimen of 5 drugs, namely, (Kanamycin (Km), Ethionamide (Ehio), Levofloxacin (Lfx), Cycloserine (Cs), Pyrazinamide (Z) and Ethambutol (E) for 5 months which was extended for 1 month more. The regimen was followed by a combination of four drugs, Ethio, Lfx, Cs, E (Ethionamide, Levofloxacin, Cycloserine, and Ethambutol) for 6 months. After a total of 12 months of therapy of multi-drug regimen, a diagnosis of extensive drug resistance (XDR) tuberculosis was made in routine drug sensitivity testing. According to the guideline, the patient was shifted to a BDQ regimen with 400 mg/day for 2 weeks, followed

by 200 mg thrice a week for 22 weeks along with another background regimen, namely Ethambutol (E), Amikacin (Am), Cycloserin (Cs), Ethionamide (Ethio), Para Amino Salicylic acid (PAS) and Pyridoxine, for 24 months. After 24 months of this therapy, the patient was declared clinically and microbiologically cured with an appropriate microbial examination report. After 3 months of completion of therapy, the patient presented with fever, cough with expectoration, and anorexia. On sputum examination, it was found to be positive for mycobacteria. The patient was declared a case of BDQ failure. A short modified Anti tubercular regimen was started with Mfx, Lzd, Z, E, Ethio, and pyridoxine (Moxifloxacin in high doses, Linezolide, Pyrizinamide, Ethambutol, Ethionamide and Pyridoxine). After 3 months of modified therapy, on investigation, sputum culture was 2+ with radiological reports showing left lung haziness with cavitation. The patient was found to be resistant to INH, R, and Lfx. After the sensitivity report, the patient was put on a salvage regimen with Delamanid (DLM, E, Am, Cs, Ethio, PAS, and Pyridoxine). After 1 and a half months of salvage therapy on investigation, TSH levels of the patient were found to be high with an increase of 3.99–7.48. Furthermore, the patient's calcium level decreased from 9.1 to 8. The patient had completed the Delamanid regimen (100 mg twice daily for 2 months followed by 200 mg once daily for 4 months). The patient died in 2021. No history of tuberculosis could be found in other family members.

CASE REPORT 2

A 37-year-old male patient weighing 44 kg was treated with various anti-tubercular regimens from the year 2000 according to the RNTPC PMDT program. Patient was treated with Cat-I 2H3R3Z3E3 (Isoniazide-600 mg, Rifampicin-450 mg, pyrazinamide-1500 mg, and Ethambutol-1200 mg) thrice a week for 2 months followed by 4H3R3 for 4 months. After 10 years of therapy, he was again treated with Cat-II drugs for tuberculosis (2H3R3Z3E3+ 1H3R3Z3E3 for 3 months, followed by 5H3R3E3 for 5 months). After 8 months of therapy, the patient was diagnosed being MDR and he was treated with a conventional MDR regimen (INH high dose, E, Z, Km, Mfx, Clf, and Ethio) for 5 months followed by Mfx, Cfz, Lzd, and INH for 5 months as continuation phase irregularly. As the patient was very irregular in treatment, after the completion of 11 months of therapy, the patient was diagnosed as pre-XDR failure in routine investigations. Patients were shifted to oral longer regimen of E, Cs, Ethio, PAS, and Pyridoxine for 24 months. Medicine was taken very irregularly by the patient and again patient went into pre-XDR failure which was detected in routine investigations. He was started on the BDQ regimen (BDQ 400 mg/day for 2 weeks followed by 200 mg thrice a week for 22 weeks) and other back regimens (E, Am, Cs, Ethio, PAS, and Pyridoxine) for 24 months. After 3 months follow-up of therapy, the patient was diagnosed with BDQ regimen failure by sputum culture which was positive, and radiological reports showing evidence of bilateral upper zone lung haziness. The patient was found to be resistant to INH, R, Mfx, and Lfx. After the sensitivity report, the patient was put on a salvage regimen with E, Z, Cfz, Cs, Pyridoxine, and other symptomatic treatment. The patient had taken a DLM regimen(100 mg twice daily for 2 months followed by 200 mg once daily for 4 months) for 6 months. The patient died in 2022. There was no family history of TB.

CASE REPORT 3

According to RNTCP PMDTprogram, a 35-year-old male of 39 kg was put on anti-tuberculous therapy from the year 2015. The patient was treated with Cat-I (INH-600 mg, R-450 mg, Z-1500 mg, and E-1200 mg) thrice a week for 6 months. After 6 months of therapy, the patient was diagnosed with MDR and treated with a conventional MDR regimen (INH high dose, E, Z, Km, Mfz, Cfz, and Ethio for 5 months followed by Mfz, Cfz, Lzd, and INH for 6 months (as continuation phase) for 11 months. The patient was declared cured with a conventional MDR regimen. After 5 years of completion of this therapy, the patient was diagnosed with XDR tuberculosis. After diagnosis, the patient was provided with therapy for XDR tuberculosis with a duration of the regime of a total of 24 months (BDQ, Lfx, Mfx, Lzd, Cfz, Cs, and Z) After 1 year of completion of BDQ and Other background regimens, patient was labeled as BDQ regimen failure in follow up. This was found to be due to the result of a microbiological investigation of 11th sputum culture which was found to be positive and radiological reports showed bilateral upper zone old Koch's calcification with right middle zone cavitation of lung the. Here also patients' TSH level was found to be very high, about 103.6 and the patient was diagnosed to be HIV reactive positive as well. The patient was found to be resistant to INH, Mfx, and Lfx. After reports of sensitivity, the patient was put on DLM (100 mg twice daily for 2 months followed by 200 mg once daily for 4 months) as per national guidelines with DLM, Lzd, Z, Cfz, Cs, Pyridoxine, and other symptomatic treatment. The patient died in 2021. No family history of tuberculosis could be found.

DISCUSSION

The rapidity with which resistance to BDQ is being reported is a cause for immense concern and alarm [8]. According to the 2013 World Health Organization report on recommendations for BDQ, it has been discussed in the report that BDQ does not address the effectiveness of its companion drugs. Regimens of BDQ combined with drugs with poor bactericidal activity or poor tissue diffusion, namely Z, PAS, Cs, E, Cfz, or Aminoglycosides might not have the efficiency and potency in preventing the selection of BDQ resistance [8]. From a point of view of preventing the development of such resistance, BDQ should always be associated with at least one such drug which has both bactericidal and sterilizing activity for the full treatment duration of the patient to avoid selection of BDQ resistance by the mycobacteria. FLQ, LDZ, DLM and possibly ETH may be considered in this category since they have proven *in vivo* activity in this regard [8].

In case report 1, the patient was cooperative and completed the treatment according to the prescribed regimen and accordingly, sputum too became negative. But after 3 months of completion of BDQ regimen, sputum was again found to be positive in regular follow-up.

In case report 2, the patient was treated with drugs from Cat-I and had recovered from tuberculosis. After 10 years of completion of therapy, the patient re-infected and was again treated with Cat II, MDR, and XDR therapy.

Such cases where the patients initially become sputum culture negative, but relapse with positive cultures after 16 months of a BDQ-containing regimen, suggest that the clinical impact of such mutations could be meaningful presently and also in future cases [8].

Second, cross-resistance between BDQ and Cfz has been discovered even before BDQ was widely used. This cross-resistance is found to be represented by mutations in the *Rv*0678 and *pep*Q genes [9]. Combinations of BDQ and Cfz or any antibiotic that has an effect against mycobacterium tuberculosis only if the added additional antibiotics are not substrates for the same efflux pumps. This strategy could prove to be effective in protection from the emergence of further resistance.

Combinations of BDQ with several new drugs have been reported in various studies [9]. One such study described a patient with MDR-TB as being resistant to both BDQ and Cfz, who then goes on to rapidly develop resistance to DLM. Yet another study shows that 6.3% of MDR-TB patients without prior Cfz or BDQ exposure have isolates with *Rv0678* mutations associated with both BDQ and Cfz resistance [10,11].

In this case report series, all the patients are given treatment after drug-sensitive testing. All patients were found to be sensitive to Cfz. No cross-resistance was observed between BDQ and R, INH, Z, S, E, Am, or Mfz [12]. Combination of BDQ with drugs found to be habitual CYP3A4 inducers or inhibitors requires extreme caution. Patients of TB/HIV co-infection also require anti-retroviral therapy during TB treatment. Lopinavir/Ritonavir, being a potent inhibitor of CYP3A4, as in Case-3, the patient is on anti-HIV drugs (Tenofovir, Lamivudine,

Atazanavir, and Ritonavir). There are significantly increased plasma BDQ concentrations and its *N*-monodesmethyl metabolite (M2); due to which enhanced toxicity from BDQ might be experienced [13]. Rifampicin and Rifabutine significantly reduces concentration of BDQ as BDQ is metabolized by CYP3A4 enzyme [14].

In Case-1 and Case-3, TSH levels were found to be excessively elevated. Hypothyroidism is a known side effect of Ethionamide (Ethio) and PAS. Hypothyroidism has vague and non-specific symptoms which can be easily missed in the case of tuberculosis where the focus is on finding signs and symptoms of tuberculosis and making a correlation with such findings [15].

In our study, TSH was repeated after the baseline test (after they were found to be altered) and it was based on clinicians' decision. These tests are not done routinely in MDR or XDR tuberculosis. Hypothyroidism has non-specific symptoms (fatigue, cold intolerance, dry skin, constipation, unexplained weight gain, menstrual disturbances, depression, etc.). These might be easily missed by the treating clinicians or could be confused with the side effects of other second-line drugs. The WHO guidelines recommend screening for hypothyroidism at 6–9 months after initiation of MDR-TB treatment [16].

BDQ should be concomitantly taken with food since this co-administration increases drug exposure. In patients with tuberculosis, psycho-social support becomes an important parameter for adherence to therapy [17]. Of the present case report series, patients from two such were divorced and living with relatives. There was a severe deficit in adequate psychological support for their long journey of disease cure. Non-adherence to long-term therapy is one of the major problems, which leads to poor treatment outcomes due to the high risk of treatment failure and long-term consequences of increasing disease transmission. Non-adherence to TB treatment can also result in the occurrence of multidrug resistance [17].

Patients of MDR/XDR-TB who are on long-term Cycloserin therapy for a long time, the drug could also affect moods. Patients who contract tuberculosis are already undernourished and in such patients, Basal Metabolic Rate rises to 14% of normal person [18]. Hence, patients' food requirements are further increased, but the patients are not able to eat proper meals may be due to disease, drugs, or lack of psycho-social support.

CONCLUSION

After the addition of BDQ to the therapy of MDR and XDR-TB, there have been almost regular and continuous reports of increased culture conversion and improved and favorable outcomes to patients' conditions. Prevention of acquired resistance to BDQ and optimal use of such resourceful drugs is extremely important to reaching the long-term goal of eradication of tuberculosis. This should be taken up on a war footing despite the process being challenging and complicated.

Current evidence suggests both BDQ and DLM offer fresh opportunities for successful management and therapy of tuberculosis. Combinations of regimens in which the addition of both BDQ and DLM is present might be considered to prevent the emergence of resistance to these new resourceful drugs [19].

Accordingly, since the rational use of new drugs (aimed at protecting both the patient and the drug) is an internationally agreed milestone, the simultaneous use of DLM and (not only BDQ) might be considered. If several conditions are to be met, ineffective treatment cannot be designed using only one new drug in addition to the optimized background regimen [19].

In the long journey of therapy for TB, if the patient is detected with drug resistance, the patient should be kept in isolation in the hospital, and proper care, nutrition, and treatment should be provided by health-care staff under observation during the entire treatment till the patient is cured from TB. This will take us nearer to the vision of TB eradication in our country in the long run.

CONSENT

Written consent was taken from all three patients before the start of data collection.

AUTHORS CONTRIBUTIONS

Dr. SM Malek and Dr. Anita Sinha Idea, collection of data. Dr. SM Malek and Dr. Anita Sinha Drafting and analysis. Dr. Anita Sinha and Dr. Anil Singh Editing and critical input.

DECLARATION OF INTEREST

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