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Study of Adverse Drug Reactions related to Pre Extremely Drug Resistant and Extremely Drug Resistant Tuberculosis on Bedaquiline drug within 14 days of admission

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Abstract **Original Research Article**

Background: Globally out of 600,000 cases of rifampicin-resistant tuberculosis about 190,000 people died from multidrug-resistant tuberculosis. New class of anti TB drug bedaquiline (BDQ) has shown efficacy in pre-extremely drug resistant (pre XDR) and extremely drug resistant (xdr) patients. ***Objectives:*** 1. To evaluate tolerability of bedaquiline in combination with background regimen (BR) for treatment of preXDR and XDR TB and observing incidence of subjects with emergence of type of adverse events in the form (mild, serious and required discontinuation of bedaquiline, 2. To observe the adverse reactions of bedaquiline for 14 days after starting bedaquiline, 3. To assess the factors (comorbidity) responsible for causing increase in adverse reactions or event for bedaquiline, 4. To assess clinical outcome at end of 14 days (at the end of first 2 weeks of bedaquiline therapy) in form of favourable and unfavourable clinical response. ***Material and Methods:*** This observational study was carried out in Department of Respiratory Medicine Dr. Vasant rao Pawar Medical College and tertiary health care institute with the duration of study from April 2019 to December 2019 with sample size 50. All patients aged > 18 years with pulmonary Tb with preXDR and XDR which were admitted at DR-TB ward in tertiary health care centre were evaluated. After complete pretreatment evaluation, according to RNTCP guideline, all patients started bedaquiline to all pre XDR and XDR patients. Tablets were given with food. Intake of bedaquiline and BR was supervised with direct observation and patients were monitored for 14 days (daily). Patients were assessed for adverse events, vital signs, ECG and clinically and were assessed daily for any adverse reactions for 14 days. All events were recorded, ECGs of all patients were taken at alternate days and sputum of all patients was sent for culture. ***Statistical analysis:*** Measurements were expressed as means and standard deviations for continuous variables and percentages for categorical variables and was analyzed. ***Results:*** Total 50 patient participated in the study. Majority of patients were less than 35 years that 72%. Males were 28 (56%) and females were 22 (44%). Majority of the study subjects has muscle wasting (96%) followed by Diabetes mellitus (12%) and liver disease (10%). 6 (12%) were smokers and 4 (8%) were used to consume alcohol. 56% of vomiting and gastritis which were the most common side effect. Other side effects such as nausea (48%), skin rash (30%), peripheral neuropathy (18%),mouth ulcer (6%), diarrhea(6%), palpitation (5%), QTC prolongation (4%), constipation (4%), headache (2%) were noted among patients. 44 (88%) clinically improved after 14 days of bedaquiline treatment. Only in 2 (4%) patients bedaquiline was stopped for its adverse reactions. ***Conclusion:*** treatment of patients with Pre-XDR as well as XDR with bedaquiline use, was generally effective and well tolerated. However, patients treated should be carefully monitored for QTcF prolongation.

Keywords: PRE XDR TB - pre extensive drug resistance tuberculosis, XDR TB – extensive drug resistance tuberculosis, ADR - adverse drug reactions, Bedaquiline.

INTRODUCTION

Globally out of 600,000 cases of rifampicin-resistant tuberculosis about 190,000 people died from multidrug-resistant tuberculosis [1]. While in 2016, globally there was about 4.1% of new cases and 19% of previously treated cases with MDR/RR-TB globally and also according to Drug resistance surveillance data

240,000 people died from MDR/RR-TB in and the number of MDR/RR-TB cases detected reached 153,000 even though there is increased testing. Also 8,000 patients with extensively drug-resistant TB (XDR-TB) were reported worldwide in 2016 and about 6.2% of people with MDR-TB have XDR-TB [2]. Rifampicin-resistant tuberculosis can be one of the following - rifampicin mono-resistant, multidrug-resistant (that is, resistant to both rifampicin and isoniazid), extensively drug-resistant (that is, multidrug-resistant plus resistance to fluoro-quinolones and second-line injectable drugs), or pre-extensively drug-resistant Pre xdr (multidrug-resistant plus resistance to either a fluoroquinolone or a second-line injectable drug) [3].

Recent report of WHO showed that only 54% of MDR or rifampicin resistance and 30% of XDR TB were successfully treated[1] and Death rate due to TB in India is nearly 28 per 1,00,000 population, which is the highest death rate among all other communicable diseases [4]. New class of anti TB drug bedaquiline (BDQ) is a diarylquinoline class of antitubercular drug that inhibits the activity of mycobacterial ATP synthase enzyme by binding to the subunit c of the proteiN [5, 6] it has strong bactericidal and sterilizing activity and is highly plasma protein bound and has extended half-life of 5.5 months is metabolized in the liver and is eliminated mainly in faeces [6-8]. The BDQ is given along with other drugs as per optimized background regimen (OBR) on a dose of 400mg per day orally for two weeks, followed by 200 mg/day on alternate days for the next 22 weeks [6]. The maximum dose not to exceed 600mg per week [7]. Further, after completion of the 24 weeks of BDQ, MDR-TB regimen will be continued as per revised national TB treatment guidelines. Adverse drug reactions (ADR) with BDQ therapy are nausea (30%), arthralgia (26%), headache (22%), haemoptysis (14%), chest pain (9%), anorexia (7%) and rash (6%)[8]. Serious adverse effects included elevated serum transaminase levels and prolongation of QT interval on ECG [6, 8].

Stage 1 phase 2b clinical trial results showed a significant increase in sputum conversion rate from 9 to 48%, when bedaquiline was added to optimised background regimen, with no significant increase in the frequency or severity of adverse drug reactions [9]. In stage 2 of the TMC207-C208 study, a phase 2b study in which bedaquiline was administered for 24 weeks to a larger number of patients, the time to sputum-culture conversion, the rates of culture conversion and drug resistance, pharmacokinetics, and safety over a 120-week period in patients receiving a preferred five-drug background regimen was evaluated and found out significant imbalance in mortality in the two treatment arms but none of the deaths in the bedaquiline arm were attributed to bedaquiline [9]. As bedaquiline is new antituberculous drug, and we started to use in our tertiary care centre since 2018. Also it was mandatory to give bedaquiline under observation hence we admitted those patients and have studied for its adverse reactions and assessed its tolerability for pre XDR and XDR TB patients in DR TB ward. Improved outcomes and reduced toxicity of MDR/XDR-TB treatment is due to the advent of new drug bedaquiline and a rapid increase in the evidence supporting the use of bedaquiline will provide additional treatment options for these patients [10]. After going through all the above studies, we at our health care centre have studied for ADR and efficacy of bedaquiline pre-xdr and xdr patients in DR TB ward.

OBJECTIVES

- To evaluate tolerability of bedaquiline in combination with background regimen (BR) for treatment of preXDR and XDR TB and observing incidence of subjects with emergence of type of adverse events in the form (mild, serious and required discontinuation of bedaquiline)
- To observe the adverse reactions of bedaquiline for 14 days after starting bedaquiline.
- To assess the factors (comorbidity) responsible for causing increase in adverse reactions or event for bedaquiline.
- To assess clinical outcome at end of 14 days (at the end of first 2 weeks of bedaquiline therapy) in form of favourable and unfavourable clinical response.

METHODOLOGY

This observational study was carried out in Department of Respiratory Medicine Dr. Vasant rao Pawar Medical College and tertiary health care institute with the duration of study from April 2019 to December 2019 with sample size 50.

All patients aged > 18 years with pulmonary Tb with preXDR and XDR which were admitted at DR-TB ward in tertiary health care centre were evaluated according to RNTCP guidelines by doing investigations such as CBC, SGPT, SGOT, Serum amylase, serum lipase, serum calcium, serum potassium, serum magnesium and ECG. Those patients whose all above investigations were within normal limit were referred for psychiatric evaluation and audiometry is done before starting bedaquiline. After complete pretreatment evaluation, according to RNTCP guideline, we started bedaquiline to all pre XDR and XDR patients. Tablets were given with food. Intake of bedaquiline and BR was supervised with direct observation and patients were monitored for 14 days (daily). Patients were assessed for adverse events, vital signs, ECG and clinically and were assessed daily for any adverse reactions for 14 days. All events were recorded, ECGs of all patients were taken at alternate days and sputum of all patients was sent for culture. Female with pregnancy or on oral contraceptives, breast feeding was excluded from our study.

Detail clinical history including past history of diabetes, hypertension, cardiac diseases, HIV infection was taken. HIV infected patients with serious illness and having CD_4 counts <250 were excluded, complicated pulmonary tuberculosis and extrapulmonary tuberculosis, significant cardiac arrthymias, patients requiring special medicines, patients having QTcf > 500 ms, history of risk factors of torsare de pointes were excluded.

STATISTICAL ANALYSIS

Measurements were expressed as means and standard deviations for continuous variables and percentages for categorical variables and was analyzed. Chi square test was used as test of significant.

Ethical considerations

The study was conducted according to the Declaration of Helsinki; the protocol was reviewed and approved by the institutional ethics committee of the institute. A written informed consent was taken from all patients after explaining the procedure**.**

RESULTS

Total 50 patients participated in the study. Majority of patients were less than 35 years that 72%. Males were 28 (56%) and females were 22 (44%).

Table-1: Age-group wise distribution of study subjects

Age group	No. of patients	Percent
≤ 25 years	15	30 %
26 to 35 years	21	42 %
36 to 45 years	5	10 %
≥ 46 years	9	18 %
Total	50	100 %

As seen in the above table and bar diagram, most of the study population belonged to the age group of 26 to 35 years (42%) followed by 36 to 45 years (10%), ≤ 25 years (30%) and ≥ 46 years (9.3%).

Table-2: Drug resistant pattern among study subjects

Drug resistant pattern	No.of patients	percentage
PreXDR with fluoroquinolone	44	88%
PreXDR with Second line injectable	3	6%
XDR (floroquinolone +Second line injectable)	3	6%
Total no.patients	50	100%

Drug resistant pattern of PreXDR with floroquinolone, PreXDR with Second line injectable and XDR (floroquinolone +Second line injectable) were 88%,6% and 6% of study population respectively.

Table-3: HIV status amongst study subjects

HIV status	No. of patients	Percent
Non-Reactive	49	98 %
Reactive	1	2 %
Total	50	100 %

As seen in the above table and bar diagram, 2% of study population that is only one patient was HIV reactive.

Table-4: Distribution of Comorbidities in study subjects

Co morbidities	no of patients	Percentage
Diabetes mellitus	6	12 %
Hypertension	2	4 %
HIV	1	2 %
Muscle wasting	48	96 %
Renal diseases	2	4 %
Liver diseases	5	10 %

Majority of the study subjects has muscle wasting (96%) followed by Diabetes mellitus (12%) and liver disease (10%). 6 (12%) were smokers and 4 (8%) were used to consume alcohol.

Table-5: Distribution of Adverse Drug Reactions in study subjects

Adverse drug reactions	No of patients	percentage
Nausea	24	48%
Vomiting	28	56%
Headache	1	2%
constipation	2	4%
Peripheral neuropathy	9	18%
Diarrhoea	3	6%
Qtc prolongation	2	4%
Mouth ulcer	3	6%
Acne	15	30%
Palpitation	5	10%
Abdomen pain	6	12%
Arthralgia	2	4%

Out of 50 patients, 56% of vomiting and gastritis which were the most common side effect. Other side effects such as nausea (48%), skin rash (30%), peripheral neuropathy (18%), mouth ulcer (6%), diarrhea (6%), palpitation (5%),QTC prolongation (4%), constipation (4%), headache (2%) were noted among patients.

Table-6: Clinical outcome after 14 days of bedaquiline treatment

Clinical outcome	Male	female	total
Clinically improved	24	20	44
Clinically not improved	4	2	6

44 (88%) clinically improved after 14 days of bedaquiline treatment

Table-7: Symptoms decreased post 14 days of treatment

Symptoms	Male	Female	total
Cough with expectoration	24	19	43
Breathlessness	22	2	24
Fever	27	21	48
Loss of appetite	18	16	34
Hemoptysis	2	1	3
Chest pain	6	7	13

Fever and Cough with expectoration was improved in majority of the patients, 48 (96%) and 43 (86%) respectively. Loss of appetite was improved in 34 (68%) patients and breathlessness was improved in 24 (48%) patients.

Table-8: Raised liver enzymes in 14 days of treatment

Liver enzymes	male	female	Total
Raised liver enzymes	4	2	6
Normal liver enzymes	24	20	44

Raised liver enzymes were raised in 6 (12%) patients

Table-9: Number of patients with QT polongation on bedaquiline

QT	male	female	total
Prolonged	1	1	2
Normal	27	21	48

Only in 2 (4%) patients QT was prolonged.

Table-12: Number of patients whose bedaquiline was stopped for its adverse reactions

Bedaquiline	male	female	total
Bedaquiline stopped	1	1	2
Bedaquiline continued	27	21	48
total	28	22	50

Only in 2 (4%) patients bedaquiline was stopped for its adverse reactions

DISCUSSION

In this study 72% of the patients belong to age group less than 35 years means younger age group subjects had Pre XDR TB or XDR TB and we found both genders have more or less equal distribution for pre XDR tb /xdr TB that is 56% and 44 % with male predominance than female.

India is a high burden country for tuberculosis (TB) and multidrug-resistant TB (MDR-TB). The World Health Organization has estimated that India accounted for 26% of the total number of TB cases worldwide in 2012, with 2.2% and 15% of the new and retreatment cases respectively being caused by multidrug-resistant strains [11]. Further, India is home to approximately 2.4 million people living with HIV [12] and considered to have a high burden on account of the large absolute numbers of people living with HIV in the country.

The dual burden of HIV and TB/DR-TB in India is significantly high with a combined rate of 5.2%, ranging from 0.4% to 28.8% in various studies, with increasing trends noted in states having a higher burden of HIV infection (13-17). However, nation-wide studies do not exist and previous studies have occurred mainly in hospitals and tertiary care centres [18-21]. A crude estimate from these studies suggests that 2500–3000 HIV-infected persons develop MDR-TB annually in India. In this study only 2% of patients was found to be seropositive (Positive HIV status)

In this study we found most of the subjects had muscle wasting (96%), 12% had history of diabetes while 4% had history of hypertension and 2% of subjects had both hypertension and diabetes, 12% of subjects were smoker and 10% subject of patients had history of liver diseases while 2% of subjects had HIV infection. A significant and positive association between DM and MDR-TB in subgroup analyses of studies DM can significantly increase the odds of developing MDR-TB in a study of article [22].

Symptoms of XDR-TB are no different from ordinary TB: a cough with thick, cloudy mucus (or sputum), sometimes with blood, for more than 2 weeks; fever, chills, and night sweats; fatigue and muscle weakness; weight loss; and in some cases shortness of breath and chest pain from study of article [23]. In this study the adverse drug reactions is as followes 48% of patients had nausea while 56 % had vomiting , headache (2%), constipation (4%), diarrhea (6%), acne(#0%) mouth ulcer (6%), palpitation (10%) abdomen pain (12%), arthralgia (4%), peripheral neuropathy (18%) and qtc prolongation (4%). Nausea and vomiting was the most common adverse drug reaction (48% and 36%) Skin rash or the formation of acne is also important adverse drug reactions (30%). In a study Rashes, in particular pustular/acneiform rashes were commonly reported. All patients were on multiple medicines that could be implicated. None of the rashes were severe [24].

At the end of 14 days of bedquiline treatment about 44% of patients clinically improved and 6 % patients didn't improve. The cause of no improvement must be due to some co morbidities as 12 % had diabetes mellitus and almost 96 % had muscle wasting. Nutrition is most important factor for good clinical improvement in TB patients. Nutritional status appears to be an important determinant of clinical outcome during tuberculosis. In an Indian study, 163 patients with tuberculosis were treated either in a sanatorium with a well-balanced diet or at home on a markedly poor diet. The overall treatment response was similar in both groups, however, those receiving better nutrition

tended to show more rapid clearance of bacteria and radiographic changes in addition to greater weight gain [25].

A recent large retrospective cohort study in South Africa compared outcomes in patients with resistant T treated with bedaquiline containing regimens to those not receiving bedaquiline and found that bedaquiline improved survival in both MDR and XDR TB [26]. Bed aquiline has a long half-life, the area under the concentration curve declined rapidly within 2–3 weeks of treatment, followed by a slow elimination [27]. Good outcomes with prolonged use of bedaquiline have recently been reported, although further data are needed to clarify this issue [10].

CONCLUSION

In conclusion, treatment of patients with Pre-XDR as well as XDR with bedaquiline use, was generally effective and well tolerated. However, patients treated should be carefully monitored for QTcF prolongation.

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