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Study of efficacy and safety of bedaquiline containing all oral longer regimen in drug resistant pulmonary tuberculosis at IRD, SMS Medical College, Jaipur.

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Abstract

Introduction: Multidrug-resistant TB (MDR) is defined as a TB patient, whose biological specimen is resistant to both isoniazid (H) and rifampicin (R) with or without resistance to other first-line anti-TB drugs. Bedaquiline along with an optimized background regimen has shown early sputum conversion in a large number of patients having drug-resistant tuberculosis. Although common side effects associated with Bedaquiline-containing regimens are nausea and hepatitis, however, the main safety concern is cardiotoxicity.

Aim: To assess the efficacy and safety of bedaquiline containing all oral longer treatment regimen for MDR/XDR PTB.

Material and Methods: A hospital-based observational study was conducted on patients having MDR/XDR PTB at the Institute of respiratory diseases, SMS Medical College, Jaipur, Rajasthan, India. 80 patients were enrolled and treated with Bdq containing all oral longer regimens and followed up for 8 months. During follow-up, efficacy in the form of sputum microscopy and culture conversion and safety by monitoring of side effects related to the regimen was assessed. The data analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 21.0.

Results: The mean age (years) of the study subjects was 33.51 ± 11.4.Majority (67.50%) patients were males. The majority (83.75%) of patients did not have any comorbidity, most of the patients were pre-XDR (50.00%), followed by MDR (45.00%). A significant increase in weight observed at the end of 6 months as

compared to baseline (p value<.0001). Sputum smear conversion at 6 months was seen in 98.55 % of patients, and sputum culture conversion at 6 months was seen in 97.10% of patients. 86.25% of patients were completely followed up. The proportion of patients with positive sputum culture for MTB at 3 months was significantly higher in immunocompromised. (p value=0.008). The most common adverse event observed was skin discoloration in 61.11% followed by peripheral neuropathy in 55.56% and arthralgia in 27.78%. QTc prolongation >500ms was seen only in 1 patient.

Conclusion: This study concluded that Bedaquiline with an optimized background regimen is more effective in early and higher sputum culture conversion rates. The majority of adverse effects are known side effects of drugs other than bedaquiline in the regimen. This regimen also has better patient tolerability and compliance.

Keywords: Bedaquiline, Delamanid, Tuberculosis, Interquartile Range

Introduction

Tuberculosis (TB) is a major health problem worldwide, with India having the highest-burden accounting for one-fourth of the global incidence. Multidrug-resistant TB (MDR) is defined as a TB patient, whose biological specimen is resistant to both isoniazid (H) and rifampicin (R) with or without resistance to other first-line anti-TB drugs. Extensively drug-resistant TB (XDR) is defined as TB caused by Mycobacterium tuberculosis strains that full fill the definition of MDR/RR-TB and are also resistant to any fluoroquinolone(FQ) (levofloxacin or moxifloxacin) and at least one additional Group A drug (presently to either Bedaquiline or linezolid [or both].

Till 2020, as many as 22,729 and 652 patients were put on Bedaquiline (Bdq) and Delamanid (Dlm)-containing regimens respectively. The success rate of patients (extensively drug-resistant [XDR] & MDR/RR-TB with additional resistance to fluoroquinolones (FQ) or injectable (SLDs) treated under Bedaquiline conditional access program (Bedaquiline -Cap) was 71% (2016–17 cohort)[1,2,3]

Bedaquiline along with an optimized background regimen has shown early sputum conversion in a large number of patients having drug-resistant tuberculosis.[4]

Although there are some side effects associated with Bedaquiline-containing regimens like nausea and hepatitis. However, the main safety concern is cardiotoxicity. Although no serious cardiac events or arrhythmias have been reported to date, Bdq has been shown to prolong the QT interval and the association with other drugs (such as clofazimine or moxifloxacin) can enhance this effect but discontinuation of Bdq due to these side effects is uncommon.[5]

The purpose of present study was to investigate the efficacy and safety of Bedaquiline-containing all oral longer treatment regimen for MDR-TB along with other background regimen.

Material and Methods

This was a hospital based observational cohort study conducted on MDR pulmonary TB patients who were eligible for Bdq containing All oral longer regimen attending at Institute of respiratory diseases, SMS medical college, Jaipur, over a period of one year (2020-2021).The study was initiated after approval from the Research Review Board (RRB) and Institutional Ethics Committee (EC).After giving a full explanation regarding the study, written consent was obtained from all enrolled patients.

Inclusion and exclusion criteria

80 patients of MDR PTB diagnosed by RT-PCR or culture of sputum (78 patients),or Bronchoalveolar lavage (2 patients) and age >18 years were recruited

after excluding patients having extra pulmonary tuberculosis, pregnancy and patients not eligible to receive bedaquiline as per latest PMDT guidelines.

All selected patients were subjected to pre-treatment evaluation before initiation of the regimen which includes- clinical evaluation (clinical history, height, weight) and laboratory-based evaluation. Laboratory-based evaluation includes- random blood sugar, HIV testing, complete blood count, liver function tests, kidney function tests, serum electrolytes (Na, K, Mg, Ca), TSH, urine examination (routine and microscopy), urine pregnancy test (in women of reproductive age group), chest X-ray, ECG, ophthalmologist opinion.

After pre-treatment evaluation, Bedaquiline-containing AOL regimen (Bdq, FQ(Lfx, Mfx), Linezolid, clofazimine, and cycloserine) was initiated in eligible patients.

Patients were followed up till 8 months clinically and microbiologically. Follow-up sputum microscopy and culture were obtained at 3 months then monthly till sputum conversion or till 6/7/8 months whichever was earlier and quarterly after conversion. Clinical evaluation was performed monthly till 6 months. ECG monitoring was done monthly or as required after two weeks. LFT was done quarterly or as and when clinically indicated. Other investigations were done as and when clinically required.

Statistical Analysis

The Categorical variables were presented in the form of numbers and percentages (%). On the other hand, the quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (Interquartile range). The statistical tests applied for the results were **(**1) Paired t-test was used for the comparison of variables that were quantitative in nature across follow up **(**2) The comparison of the variables which were qualitative in nature were analyzed using a Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used. The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 21.0.For statistical significance, a p-value of less than 0.05 was considered statistically significant.

Results and Observation

The mean age (years) of the study subjects was 33.51 ± 11.4. Majority (67.50%) patients were males. Majority (83.75%) of patients did not have any comorbidity, 8(10%) patients were diabetic, and only 5 out of 80 patients (6.25%) were HIV positive. Most of the patients were pre-XDR (50.00%), followed by MDR (45.00%).

Majority (86.25%) of patients were completely followed up. 4 patients were lost to follow-up during the study period and in2 patients follow-upsputum specimens could not be obtained due to dry cough. Bedaquiline was stopped due to QTc prolongation in only one patient. Total 4 patients died during the course of treatment due to respiratory failure.

The mean value of weight at the initiation of treatment, end of 6 months, and increase in weight of study subjects was 45.31 ± 9.69, 50.37 ± 9.39, and 4.46 ± 2.96respectively. A significant increase in weight was observed at the end of 6 months as compared to baseline. (p value<.0001).

Sputum microscopy for AFB at 3 months was positive in only 16 out of 69 patients (23.19%) and positive in only 1 out of 69 patients (1.45%) at 6 months. Sputum culture at 3 months was negative in majority (49(72.06%)) of patients. Culture conversion at 6 months was seen in 97.10% of patients.

The proportion of patients with positive sputum culture at 3 months was significantly higher in

immunocompromised as compared to patients without comorbidities (63.64% vs 21.05% respectively). (p value=0.008). Only one patient required a repeat sample for culture at 3 months.

The most common side effect observed with Bdq containing regimen was skin discoloration in 61.11% of patients followed by peripheral neuropathy in 55.56% and arthralgia in 27.78%.Nausea and vomiting were observed in 26.39%of patients. QTc prolongation was observed in7 patients. Among them, 6 patients had QTc values between 480-500 ms, and only one patient had >500 ms.

Table 1: Demographic and clinical characteristics of study subjects.

Demographic characteristics	Frequency	Percentage
Gender		
Female	26	32.50%
Male	54	67.50%
Age(years)		
Mean ± SD	33.51 ± 11.4	
Median(25th-75th percentile)	30(23.75-42.25)	
Range	18-64	
Immunocompromised status		
No comorbidities	67	83.75%
Diabetes mellitus	8	10.00%
HIV	5	6.25%
Total	80	100.00%
Drug sensitivity profile		
Pre-XDR	42	52.50%
XDR	2	2.50%
MDR	36	45.00%
Total	80	100.00%

Table 2: Descriptive statistics of weight (kg) of study subjects.

Weight(kg)	Mean ± SD	Median(25th-75th percentile)	Range	P value
Initiation of Rx	45.31 ± 9.69	44.5(40-51)	25-72	<0.0001
End of 6 months	50.37 ± 9.39	50(42.5-57)	31-75	
Increase in weight	4.46 ± 2.96	4(2-6)	-2-13	-

Paired t-test

Table 3: Follow-upsputum microscopy for AFB and sputum culture for MTB of study subjects.

Sputum microscopy for AFB	Frequency	Percentage
At 3 months		
Negative	53	76.81%
Positive	16	23.19%
At 6 months		
Negative	68	98.55%
Positive	1	1.45%
Sputum culture for MTB		
At 3 months		
Negative	49	72.06%
Positive	19	27.94%
At 6 months		
Negative	67	97.10%
Positive	2	2.90%

Table 4: Sputum culture conversion for MTB with immunocompromised status.

Sputum culture for MTB	Immunocompromised	No comorbidities	Total	P value
At 3 months				
Negative	4 (36.36%)	45 (78.95%)	49 (72.06%)	0.008*
Positive	7 (63.64%)	12 (21.05%)	19 (27.94%)	
At 6 months				
Negative	11 (91.67%)	56 (98.25%)	67 (97.10%)	0.32*
Positive	1 (8.33%)	1 (1.75%)	2 (2.90%)	

* Fisher's exact test

Table 5: Adverse drug events in study subjects.

Adverse drug effects	Frequency	Percentage
Skin		
Skin discolorations	44	61.11%
Itching and rashes	2	2.78%
Gastrointestinal		
Nausea and vomiting	19	26.39%

Pain abdomen and diarrhoea	2	2.78%
Hepatitis	6	8.33%
Peripheral neuropathy	40	55.56%
Arthralgia	20	27.78%
Neurological		
Depression	3	4.17%
Psychosis	1	1.39%
Seizure	1	1.39%
Hematological		
Thrombocytopenia	5	6.94%
Anemia	3	4.17%
Eye	8	11.11%
Hearing loss	4	5.56%
QTc prolongation	7	9.46%

Discussion

India is a global 'hotspot' for MDR-TB and bedaquiline is a novel drug that emerged for the treatment of drug-resistant tuberculosis. This emphasizes the importance of rapid diagnosis, effective treatment, and source control of MDR-TB especially in economically productive age groups in the resource's poor country like India.

In our study group, most patients were male and younger age group with no immunocompromised state. A significant increase in weight was observed at the end of 6 months as compared to weight at the initiation. (p value<.0001).

The Interim analysis of sputum microscopy for this cohort of MDR-TB patients showed that majority (76.81%) of patients achieved sputum smear conversion at 3 months. Furthermore 98.55% of patients achieved smear conversion at 6 months. which showed early and higher smear conversion rates with this regimen. Sarin, et al. observed similar results in his study.[4]

The Interim outcome of sputum culture conversion for this cohort of MDR-TB patients shows that in the majority (72.06%) patient's culture conversion was achieved at 3 months, while culture conversion was achieved in 97.10% of patients at 6 months. Such results were much more favourable than those observed in large cohorts of patients with MDR TB in the pre-bedaquiline era (with success rates of 54%–58% and death rates of 13.8%–15%)[6,7], thus indicating a beneficial effect of the addition of bedaquiline to background MDR/XDR TB regimens. Mbuagbaw et al also found a cure rate of 60.1% (95% CI 50.2%–69.2%; I2 = 66%); treatment success, 65.8% (95% CI 59.9%– 71.3%; I2 = 38%); and treatment failure, 5.1% (95% CI 1.6%–14.8%; I2 = 73%) in his study.[5]

In our study Majority, (86.25%) of patients were completely followed up. 4 patients were lost to follow up and 4 patients died during the study period. The cause of death was related to extensive pulmonary involvement, septicemia, and respiratory failure. The lower mortality was observed in our study also strengthens the use of bedaquiline in patients with MDR TB.

Our study adds some information about the use of bedaquiline in persons living with HIV and DM. Favourable outcomes may be more challenging to achieve in these patients. The proportion of patients with positive sputum culture for MTB at 3 months was significantly higher in immunocompromised patients.[8]Reason for this disparity may be due to low CD4 count, extensive pulmonary involvement, poor glycaemic control, and poor general condition of our study patients.

The majority of the adverse effects were easily identifiable, reversible, and related to clofazimine (hyperpigmentation) and linezolid (anaemia) rather than BDQ. Peripheral neuropathy was higher than in the BEAT study, [(5)] probably due to factors such as alcohol abuse, malnutrition, or diabetes mellitus in our study subjects.

Only one patient in our study had the highest recorded value of QTcF >500 ms without arrhythmia, this could be due to the concomitant use of 3 potentially QT-influencing drugs. Other studies have found similarly lower rates of cardiotoxicity[5]. This finding could therefore alleviate some of the concerns about the risk for cardiotoxicity related to the use of bedaquiline and this will reduce physicians' apprehension about using BDQ-containing regimens in nonhospital settings due to cardiotoxicity concerns.

Overall, our study suggests that bedaquiline should be included in all the regimens for the treatment of MDR/XDR TB, for not only its additive value in culture conversion and treatment success but also its safety in varied settings.

Limitation

This was an observational study conducted under programmatic conditions hence the data was not collected under research mode. Also, follow-up in our study was done for 8 months however large sample size and long-term follow-up would be needed to determine the final outcome and long-term adverse events for this regimen. Similarly, many factors also influence the treatment outcome like the radiological extent of the disease, tolerability of drugs, etc which were not included in our study.

Conclusion

This study concluded that Bedaquiline with an optimized background regimen is more effective in early and higher sputum culture conversion rates as compared with previous data available for other regimens without Bedaquiline in drug-resistant tuberculosis. Adverse drug events do occur with this regimen but are manageable. The majority of adverse effects are known side effects of drugs other than bedaquiline in the regimen. This regimen also has better patient tolerability and compliance. A better outcome for MDR-TB patients requires strengthening of infrastructure in terms of early suspicion and diagnosis of MDR tuberculosis, availability of effective regimen, regular follow up, and training the peripheral staff for early identification and management of common adverse drug reactions.

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