Original Article

DOI: 10.7860/JCDR/2022/52307.16041

QT Changes of Unforeseen Implications and Bedaquiline: An Observational Study

Internal Medicine Section

SAMYA DUTTA[1], CHITRITA GHOSH[2], SANDIP MUKHOPADHYAY[3], TA RUPAM KUMAR[4]

ABSTRACT

Introduction: Bedaquiline (BDQ), a diarylquinoline class of antimicrobial, is one of the latest anti-mycobacterial agents to be developed in several decades. Despite the drug being a great hope for the Drug Resistant Tuberculosis (DR-TB) patients, previous studies have raised alarm about BDQ-induced QT prolongations of serious clinical implication. Unfortunately, knowledge about adverse drug reaction of BDQ on Indian patients remains limited. Therefore, dedicated research focused on safety of BDQ in Indian population can provide valuable insight.

Aim: To assess the short-term safety of BDQ on Indian DR-TB patients.

Materials and Methods: This prospective observational study was conducted over a period of one year on 49 DR-TB patients under BDQ therapy. Data of all the DR-TB patients from the first 14 days of BDQ therapy were enrolled in the study. All adverse events during this period were closely observed and recorded. Electrocardiography (ECG) were recorded daily during this period. From the observed QT value, a 'corrected QT' (QTc) value was calculated using Fridericia's formula (QTcF). Values above 440 ms were noted as prolonged QTcF and values >500 ms were given a special consideration.

Results: Total 49 patients were recruited in the present study, with mean age of 38.63±1.63 years. A total of 124 reports of adverse events or symptoms were recorded during the 14 days in-hospital period. Nausea was the most commonly reported complaint (n=33) followed by headache (n=30) and arthralgia (n=28). A total of 278 observations of prolonged QTcF values (>440 ms) was noted out of 686 ECG recordings. The mean QTcF values among day 1, day 7 and day 14 showed statistically significant difference {p=0.01, 95% CI (Confidence Interval)}. Moreover, a mean increase of 14.2% was observed in the QTcF values between day 1 and day 14. There were a total of 69 observations of QTcF value more than 500 ms. The incidence of such value was maximum on day 14 (n=9). The QTcF values were found to follow three distinct trends: a) Initial rise then fall (n=9), b) Initial fall and then rise (n=10) and c) Rise followed by further rise (n=30).

Conclusion: The present observational study was targeted to detect the short-term safety of BDQ in the DR-TB patients during the initial 14 days of therapy. The patients complained of several non serious adverse effects. Three distinct patterns of QT changes and reduction of QTcF values were relatively new findings with the merit for further investigation. However, a longer perspective of adverse events was beyond the scope of this study.

Keywords: Drug-resistant tuberculosis, QT prolongation, QT reduction

INTRODUCTION

Tuberculosis (TB) has been found to affect more than 10 million people globally in 2017 and approximately 1.5 million people died out of TB from all over the world in 2018 [1,2]. Moreover, emergence of DR-TB has become a threat to the global community. It was found that 20% of the previously treated cases and 3% newly diagnosed cases were Multi Drug Resistant TB (MDR-TB) [2]. Additionally, Extensively Drug Resistant TB (XDR-TB) is now reported from 105 countries and approximately 9.7% MDR-TB patients are actually XDR [1]. Further alarm was raised from a study in South Africa which found that only 56% MDR-TB patients could be treated successfully and hence, MDR-TB constitutes 1/3rd of the total deaths from antimicrobial resistance globally [3]. Therefore, the need for new and effective drugs to treat such patients is the need of the day.

Bedaquiline (BDQ), a diarylquinoline class of antimicrobial, is one of the latest anti-mycobacterial agents which is developed in several decades [4-7]. This new drug demonstrated inhibitory action against the proton pump for Adenosine Triphosphate (ATP) Synthase of Mycobacterium sp [8-11]. A number of studies had been conducted in different parts of the world with BDQ and demonstrated a better 'sputum conversion' with BDQ-combining regimens compared to non BDQ regimens [12-22]. Moreover, BDQ-containing regimens were found to be more cost-effective [23].

With the data of positive results from the clinical trials, BDQ received approval in the United States of America (USA) by the Food and Drug Administration (FDA) in 2012 and in Europe by the European Medicines Agency in 2014 [24]. South Korea, South Africa, India, the Russian Federation and Peru also approved this drug by the 2014-15 [25,26]. In India, 14% previously treated and 2.4% new patients are MDR compared to global average of 20% and 3%, respectively [1,2]. However, a high burden of TB in India constituting 27% of the global TB cases prompted the relatively new drug to be incorporated into the Revised National Tuberculosis Control Program (RNTCP) in 2016 in India for MDR-TB cases in a conditional access program [2]. Though the drug appeared to be a great hope in the DR-TB patients, knowledge about adverse drug reaction profile BDQ still remains limited due to various reasons. The drug received an accelerated approval in the USA after phase 2b study [27]. Considering higher number of deaths in the BDQ arm, the drug received a black-box warning from US-FDA though the deaths could not be related to BDQ [28,29]. BDQ, though excellent in terms of the minimal inhibitory concentration, has some intricate risks for the human body like possible cardiac toxicity due to its action on the hERG (human Ether-a-go-go-Related Gene) potassium channels, possibilities of hepatic damage, phospholipidosis as well as potential drug interactions [30]. The drug is still very new in the market and use is restricted in most of the countries. There is scarcity of data from phase 4 trials as well as information from pharmacovigilance activities. India having a higher burden of TB patients has the potential to provide newer and rare adverse effect data of BDQ. Indian patients are also genetically as well as phenotypically different from the patients of other TB-burdened countries and hence there remains the possibility of the drug to act differently. Hence, dedicated research focused on safety of BDQ in Indian population can provide valuable insight to the globe which is often beyond the scope of the trails with efficacy as primary

end points. So, designing a study involving daily adverse effect data collection for initial 15 days from Institutionalised patients could be more 'real life' compared to clinical trials and might have the potential to detect newer things due to use in a 'less rigid' inclusion criteria than clinical trial. Probably, this initial phase of treatment is the time of body to respond to the new compound more 'acutely' and will have the potential to detect possible 'idiosyncratic, bizarre or novel' reactions leading to dropouts or mortalities [31].

Therefore, the present study has been planned to elicit a safety report of BDQ on the MDR-TB patients during their in 'Institutionalised treatment phase' under the 'conditional access program'.

MATERIALS AND METHODS

This was a prospective observational study on the DR-TB patients under BDQ therapy at the DR-TB centre of Burdwan Medical College located at Eastern part of India. This centre predominantly caters the patients from Eastern India and particularly from several nearby districts from the state of West Bengal. The study commenced after receiving approval from the Institutional Ethics Committee (IEC) (letter no: BMC/1544/19). The data recording and storage was anonymised and there was no personal identifier. Therefore a 'waiver of consent' was obtained from the IEC for this research. The study was conducted over a period of one year from August 2018 to July 2019.

Inclusion criteria: Data of all the MDR-TB and XDR-TB patients receiving BDQ therapy were enrolled in the study.

Exclusion criteria: Only one patient who was on a conditional access to a simultaneous administration of BDQ and delamanid was excluded from the present study.

Study Procedure

As per the conditional access protocol, the DR-TB patients who were selected for BDQ therapy were Institutionalised in the DR-TB centres for initial 14 days of treatment [32]. All MDR-TB patients with additional resistance to fluoroquinolones received the BDQ containing regimen. The regimen for MDR-TB with resistance to all fluoroquinolones used here were six months BDQ with 6-12 months Kanamycin (Km), Ethionamide (Eto), Cycloserine (Cs), Pyrazinamide (Z), Linezolid (Lzd) to be followed by 18 months of "Eto Cs Lzd E" (E: Ethambutol). The doses of BDQ were 400 mg once daily for first two weeks, then 200 mg thrice a week till completion of six months. Doses of other drugs were Km 750 mg, Eto 750 mg, Cs 750 mg, Z 1500 mg, Lzd 600 mg, Ethambutol 1200 mg once daily. The regimens used for XDR-TB were six months BDQ with 6-12 months Kanamycin (Km) or Capreomycin (Cm), Ethambutol (E), Pyrazinamide (Z), Ethionamide (Eto), Cycloserine (Cs), Linezolid (Lzd), Clofazimine (Cfz) , followed by 18 months of "Eto Cs Lzd Cfz". BDQ was used in the same dose as of MDR-TB. The doses of other drugs were Km 500 mg or Cm 750 mg, Eto 500 mg, Cs 500 mg, Z 1250 mg, E 800 mg, Lzd 600 mg, Cfz 200 mg once daily. All the patients received oral pantoprazole 40 mg twice daily, domperidone 10 mg thrice daily and vitamin B complex tablets once daily.

Baseline renal function, liver function, blood glucose investigations were done routinely before starting the treatment. Baseline ECGs were obtained from all the patients. After starting BDQ containing regimen, the patients were closely observed by attending Physicians' daily visits. Data of all such visits, laboratory tests and ECGs were recorded on real-time basis. ECGs were recorded daily during this period. All adverse events during this period were closely observed and recorded.

All baseline information related to clinical, laboratory and ECG parameters were noted for each patient. ECG recordings were evaluated for QT prolongation and other significant changes. As per the RNTCP guideline for BDQ usage, 'QTc' values were calculated from the observed QT values using the Fridericia's (QTcF) formula ($QTcF=QT/3\sqrt{(RR\ Interval)}$ [33,34]. Values above 440 ms were noted as prolonged QTcF. QTcF values >500 ms were given special consideration as they indicated cessation of therapy.

Moreover, a separate record was maintained for any report of mortality during the study period. All adverse events, reported as well as obtained from laboratory parameters and ECG recordings, were analysed for causality by WHO-UMC (World Health Organisation-Uppsala Monitoring Centre) scale. In accordance with the WHO-UMC scale, an adverse drug reaction is deemed "Certain" when it has a plausible time relationship to drug intake, which cannot be explained by any disease or other drugs, and if the dechallenge and rechallenge are satisfactory. An adverse drug reaction is termed "Probable" if it has a reasonable time relationship to drug intake and is unlikely to be attributed to any disease or other drugs, if dechallenge is clinically reasonable and if rechallenge is not required. An adverse drug reaction is called "possible" if it has a reasonable time relationship to drug intake, which could also be explained by disease or other drugs, when information on drug withdrawal may be lacking or unclear. An adverse drug reaction is termed "unlikely" if it the time to drug intake makes the relationship improbable (but not impossible), with the disease or other drugs providing plausible explanations [35].

STATISTICAL ANALYSIS

All obtained data were tabulated, and descriptive statistics were applied. The statistical differences in mean QTcF values among day 1, day 7 and day 14 of BDQ therapy were tested using repeated measures Analysis of Variance (ANOVA) test. All statistical tests were performed using International Business Machines (IBM), Statistical Package for the Social Sciences (SPSS) version 20.0.

RESULTS

Total 49 patients were recruited in the present study with mean age of 38.63±1.63 years. Gender distribution was predominantly skewed with males more than 65%. Most of them were smokers [Table/Fig-1]. Laboratory parameters mostly within normal limit except for low haemoglobin value [Table/Fig-2].

Variables	Values
Age (years)	38.63±1.63*
Gender (Male/Female)	32 (65)/17 (35)**
Marital status (Married/Unmarried)	36 (73.5)/13 (26.5)**
Smoking (Packet years)	1.8±0.26*
Diagnosis (MDR-TB+FQ resistant/XDR-TB)	43 (88)/6 (12)**

[Table/Fig-1]: Baseline demographic data of the enrolled DR-TB patients.
*Values in mean±standard error of mean (SE); **Values as n (%)

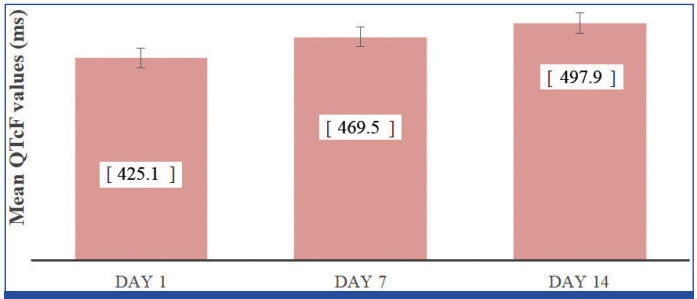
Variables	Mean±SD
Haemoglobin (g%)	9.69±0.30
Total leucocyte count (/cmm)	8295.83±239.33
Neutrophil (/cmm)	66.67±0.62
Eosinophil (/cmm)	2.94±0.12
Lymphocyte (/cmm)	26.10±0.75
Monocyte (/cmm)	2.33±0.11
Total serum bilirubin (mg%)	0.80±0.01
SGPT (IU/L)	26.52±0.47
SGOT (IU/L)	24.79±0.43
Alkaline phosphatase (IU/L)	144.96±2.69
Total protein (g%)	6.73±0.07
Albumin (g%)	3.81±0.05
Globulin (g%)	2.94±0.04
Urea (mg%)	13.48±0.42
Creatinine (mg%)	0.86±0.02
Serum Na^+ (mEq/L)	133.48±0.42

Serum K^+ (mEq/L)	3.78±0.04
Total cholesterol (mg%)	155.42±1.55
Triglyceride (mg%)	107.85±1.94
HDL (mg%)	39.38±0.69
LDL (mg%)	81.71±1.21
VLDL (mg%)	24.17±0.64
Serum uric acid (mg%)	5.81±0.08
Random blood glucose (mg/dL)	139.73±4.03

[Table/Fig-2]: Laboratory parameters of BDQ recipients.
SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein

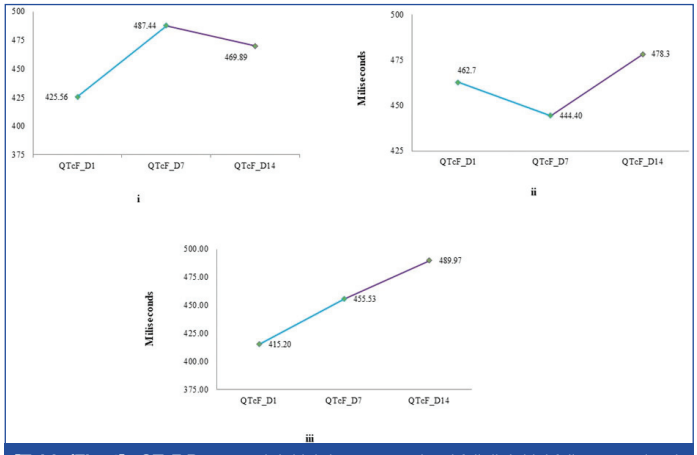
A total of 124 reports of adverse events or symptoms were recorded during the initial 14 days in-hospital period. Nausea was the most commonly reported complaint (n=33) followed by headache (n=30) and arthralgia (n=28). There were also reports of other complaints like diarrhoea (n=15), anorexia (n=9), chest pain (n=7) and haemoptysis (n=2). Among the list of complaints, nausea, headache and joint pain were chosen more frequently by the patients as their 'most troubling' or 'most pertinent' complaint.

ECG recordings were observed for QTcF value. A total of 278 observations of prolonged QTcF values (>440 ms) was noted out of 686 ECG recordings (A total of 9 observations on day 1, 86 on day 7 and 183 on day 14). The mean QTcF values among day 1, day 7 and day 14 are shown in [Table/Fig-3] and the difference among them was statistically significant (p=0.01, 95% CI).



[Table/Fig-3]: Mean QTcF change over time.

Moreover, a mean increase of 14.2% was observed in the QTcF values between day 1 and day 14. There were total of 69 observations of QTcF value more than 500 ms. The incidence of such value was maximum on day 14 (n=9). On further analysis of data, the QTcF values were found to follow three distinct trends: a) Initial rise then fall (n=9); b) Initial fall and then rise (n=10); and c) Rise followed by further rise (n=30) [Table/Fig-4].



[Table/Fig-4]: QTcF Patterns: i. Initial rise to sustained fall, ii. Initial fall to sustained rise, iii. Initial rise followed by further rise.

A subgroup analysis was carried out in these patients. Though majority patients had shown only rising trend (n=32) of QTcF value, fall in QTcF at some point of time (subgroups a and b) was noted in 34.7% patients which was an appreciable number (n=17). One patient had shown only downward trend in QTcF value from the baseline. Such fall in QTcF value was not a result of stopping any drug or adding any new therapy.

In the absence of 'dechallenge' and 'rechallenge', there was no 'certain' or 'probable' causal relationship of the adverse events. Majority of the adverse events fell under the 'possible' category [Table/Fig-5].

ADRs	Possible, n (%)	Unlikely, n (%)
QT prolongation	185 (66.5)	93 (33.5)
Tachycardia	9 (53)	8 (47)
Reported symptoms		
Nausea	29 (88)	4 (12)
Headache	28 (93)	2 (7)
Joint pain	24 (86)	4 (14)
Anaemia	4 (8)	45 (92)

[Table/Fig-5]: Causality analysis of common ADRs.

DISCUSSION

The present observational study was targeted to detect the short-term safety of BDQ in the MDR and XDR-TB patients over the initial 14 days of therapy. The patients complained of a number of adverse effects ranging from minor gastrointestinal side-effects to headache or arthralgia. However, all of these were non serious in nature. There was no major change in the laboratory parameters during these 14 days of duration. In the ECG, mean QT interval was increased. However, three distinct patterns of QT changes were noted where a subgroup of patients showed rise in QTcF values followed by a fall, another subgroup showed a fall of QTcF followed by rise and the third subgroup showed only rise in QTcF. The third pattern was more common than the previous two. Reduction of QTcF is a relatively new finding that calls for further investigation.

The pilot study, where BDQ was added to the background regimen in the first eight weeks on 23 patients reported nausea 26.1% which was most commonly. Bilateral hearing impairment, extremity pain, acne, and non cardiac chest pain were noted in 13, 21%, 17 and 13% of patients. However, the researchers commented that other than nausea, the other reported adverse events were similar to placebo [36]. During the first two weeks of initiation, nausea remained a common complaint and only few chest pains were noted in the present study.

A dose ranging study that recruited 68 treatment-naïve TB patients in two centres of South Africa of which 60 patients were subjected to BDQ alone and was conducted over a period of 14 days. Among the 57 patients who completed the study only 8 patients (13.3%) experienced at least one adverse event of mild to moderate severity [21]. The duration of follow-up of this study was similar to the present study with common findings like reported events of headache and nausea. However, the incidences of adverse events were considerably higher in the present study. It should be noted that the present study focused on real-world data where BDQ was used as an add-on therapy over a baseline antitubercular regimen, whereas the dose ranging study mentioned earlier evaluated the adverse effects of BDQ monotherapy. Multiple antitubercular drugs in the background might have enhanced the frequency of common adverse events in the present study.

In another phase II study from Japan, Treatment Emergent Adverse Events (TEAE) were noted in 83% patients. Among these TEAEs, hypoesthesia, nasopharyngitis, acne and hepatic function abnormalities were the commonest to occur [37]. These adverse events were not found in the present study. Probably, the shorter exposure of two weeks did not lead to these adverse effects.

At the time when the phase 3 trials of BDQ were going on, there were published reports of BDQ compassionate use in two XDR-TB patients

in Italy. There was no report of any nausea, vomiting or arthralgia. The authors did not notice any QT change in these two patients [18]. This finding was different from the present study. However, it should be noted that the report was only on two patients and hence, could have been inadequate to detect any adverse effect.

None of the above studies had mentioned any QT prolongation. However, the phase 2b study on 160 MDR-TB patients that preceded the conditional approval of BDQ had sufficient reports of QT prolongation. The mean QTcF was increased by 15.4 ms following 24 weeks of BDQ therapy. One patient had a single reported event of QTcF >500 ms. Though increased number of deaths was reported in the BDQ arm, the authors concluded that there was no association of such deaths to BDQ plasma concentration. The other reported adverse effects like nausea, arthralgia, headache, hyperuricaemia were similar to the placebo arm of the study [38]. The present study had a close similarity in the pattern of the non serious adverse events. However, there were a greater number of events of QTcF of >500 ms. The mean rise after two weeks was as high as 60 ms (14.2%) in the current study, but this data cannot be compared to the above mentioned study as data from the phase 2b study revealed the rise only after the 24th week.

Another report of an XDR patient where BDQ, delamanid and clofazimine were co-prescribed had a consistent rise in QTcF above 500 ms from the 5th week of therapy leading to discontinuation of clofazimine with some benefit for few weeks. In this patient, all the above three drugs have the potential to raise the QT interval. Though clofazimine was withdrawn, there was only sporadic report of cardiotoxicity with it and even after discontinuation further rise of QTcF above 500 ms probably suggests contribution of BDQ or delamanid, either alone or in combination [39].

However, there was a mark of caution from WHO about BDQ and the clinical use of BDQ is mostly supported with monitoring of ECG. A larger survey that identified 1044 BDQ-treated patients found that drug withdrawal was done in eight patients. One patient had grossly overdosed to BDQ during the continuation phase due to misconception and succumbed to a heart block which was associated with QT prolongation [40].

A systematic review further analysed the available evidence with BDQ and QT prolongation. It found that despite use in combination with other potentially arrhythmogenic drugs like fluoroquinolones or clofazimine, the increase in most cases were <20 ms. Out of total 1303 patients, QT values >500 ms were found only in 42 patients. Many centres, though conducted monthly or weekly ECG to detect the QT changes, there were inconsistency in reporting QT and also in the frequency of ECG [41]. Again reported incidences were higher in number in the present study and this could have been a result of daily ECG recordings revealing a more vivid picture of QT changes.

Though QT prolongation was noted in other studies, lowering of QT interval was not reported in the clinical trials, large cohorts, or case reports with BDQ. The subset of 19 patients who showed a reduction in QT interval in the present study, were otherwise asymptomatic. Also, the subset of patients where QT interval had shown an initial fall followed by a rise remained asymptomatic. The plasma electrolytes were within normal range during this period. There is little explanation of such events with our present knowledge. It is not known that whether such findings were missed in earlier studies due to less intense ECG monitoring or did not occur due to some other reasons including genetic background.

Limitation(s)

Small sample size was a limitation of the present study. There was also no attempt to record of efficacy. Shorter duration may be another point of criticism. However, intense and regular monitoring of adverse events and daily ECG monitoring in completely hospitalised patients definitely are some strong points in the favour of this study which were hardly ever reported in the previous studies. The study also targets to detect the short-term safety and hence a longer perspective of adverse events following BDQ is beyond the scope of the present study. Further studies are therefore recommended to explore the possible reasons behind such finding.

CONCLUSION(S)

The present study found that BDQ is generally well tolerated after initiation of therapy for MDR and XDR-TB. Asymptomatic QT prolongation over 500 ms occurs with BDQ. Reduction of QT without any associated symptoms or laboratory abnormality may be found in a subset of patients due to unknown reason. Further studies including pharmacovigilance activities are therefore, recommended to explore the novel findings.

REFERENCES

[1] WHO | Global tuberculosis report 2019 [Internet]. Geneva: World Health Organization; [cited 2020 Aug 22] p. 297. Available from: http://www.who.int/tb/publications/global_report/en/.

[2] Revised National TB Control Program Technical and Operational Guidelines for Tuberculosis Control in India 2016 [Internet]. Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India; [cited 2020 Aug 22]. Available from: https://tbcindia.gov.in/showfile.php?lid=3197.

[3] United Nations General Assembly. Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis. United Nations; 2018 [Internet]. [cited 2020 Aug 26] p. 3. Report No.: 73/3. Available from: https://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/73/3.

[4] Tiberi S, du Plessis N, Walzl G, Vjecha MJ, Rao M, Ntoumi F, et al. Tuberculosis: Progress and advances in development of new drugs, treatment regimens, and host-directed therapies. Lancet Infect Dis. 2018;18(7):e183-98.

[5] Bahuguna A, Rawat DS. An overview of new antitubercular drugs, drug candidates, and their targets. Med Res Rev. 2020;40(1):263-92.

[6] Nagabushan H, Roopadevi HS. Bedaquiline: A novel antitubercular drug for multidrug-resistant tuberculosis. J Postgrad Med. 2014;60(3):300-02.

[7] Fact Sheets | Treatment | Treatment of Multidrug-Resistant Tuberculosis: Bedaquiline | TB | CDC [Internet]. 2020 [cited 2020 Aug 22]. Available from: https://www.cdc.gov/tb/publications/factsheets/treatment/bedaquiline.htm.

[8] Rustomjee R, Diacon AH, Allen J, Venter A, Reddy C, Patientia RF, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob Agents Chemother. 2008;52(8):2831-35.

[9] Segala E, Sougakoff W, Nevejans-Chauffour A, Jarlier V, Petrella S. New mutations in the mycobacterial ATP synthase: New insights into the binding of the diarylquinoline TMC207 to the ATP synthase C-ring structure. Antimicrob Agents Chemother. 2012;56(5):2326-34.

[10] Rouan M-C, Lounis N, Gevers T, Dillen L, Gilissen R, Raoof A, et al. Pharmacokinetics and pharmacodynamics of TMC207 and its n-desmethyl metabolite in a murine model of tuberculosis. Antimicrob Agents Chemother. 2012;56(3):1444-51.

[11] Andries K, Verhasselt P, Guillemont J, Göhlmann HWH, Neefs JM, Winkler H, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. Science. 2005;307(5707):223-27.

[12] Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: A multicentre study. Eur Respir J. 2017;49(5):1700387.

[13] Guglielmetti L, Le Dû D, Jachym M, Henry B, Martin D, Caumes E, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: Interim analysis of a French cohort. Clin Infect Dis. 2015;60(2):188-94.

[14] Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014;371(8):723-32.

[15] Diacon AH, Pym A, Grobusch M, Patientia R, Rustomjee R, Page-Shipp L, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med. 2009;360(23):2397-405.

[16] Pym AS, Diacon AH, Tang SJ, Conradie F, Danilovits M, Chuchottaworn C, et al. Bedaquiline in the treatment of multidrug and extensively drug-resistant tuberculosis. Eur Respir J. 2016;47(2):564-74.

[17] Lu X, Smare C, Kambili C, El Khoury AC, Wolfson LJ. Health outcomes of bedaquiline in the treatment of multidrug-resistant tuberculosis in selected high burden countries. BMC Health Services Research. 2017;17(1):87.

[18] Tiberi S, De Lorenzo S, Centis R, Viggiani P, D'Ambrosio L, Migliori GB. Bedaquiline in MDR/XDR-TB cases: First experience on compassionate use. Eur Respir J. 2014;43(1):289-92.

[19] Ndjeka N, Conradie F, Schnippel K, Hughes J, Bantubani N, Ferreira H, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: An interim cohort analysis. Int J Tuberc Lung Dis. 2015;19(8):979-85.

[20] Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and multidrug-resistant tuberculosis: A systematic and critical analysis of the evidence. Eur Respir J. 2016;47(2):394-402.

[21] Diacon AH, Dawson R, Groote-Bidlingmaier FV, Symons G, Venter A, Donald PR, et al. Randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum microscopy smear-positive pulmonary tuberculosis. Antimicrob Agents Chemother. 2013;57(5):2199-203.
[22] Kakkar AK, Dahiya N. Bedaquiline for the treatment of resistant tuberculosis: Promises and pitfalls. Tuberculosis (Edinb). 2014;94(4):357-62.
[23] Ionescu AM, Mpobela Agnarson A, Kambili C, Metz L, Kfoury J, Wang S, et al. Bedaquiline- versus injectable-containing drug-resistant tuberculosis regimens: A cost-effectiveness analysis. Expert Rev Pharmacoecon Outcomes Res. 2018;18(6):677-89.
[24] Access: MSF reports on use of the new tuberculosis drugs bedaquiline and delamanid | MSF [Internet]. Médecins Sans Frontières (MSF) International. [cited 2020 Aug 26]. Available from: https://www.msf.org/access-msf-reports-use-new-tuberculosis-drugs-bedaquiline-and-delamanid.
[25] Stop TB Partnership | First time in decades: New antibiotic to treat Multidrug-Resistant Tuberculosis (MDR-TB) receives approval in Peru. Stop TB Partnership. Available from: http://www.stoptb.org/news/frompartners/2015/fp15_012.asp. [Accessed on: 2020 Aug 22].
[26] Salhotra VS, Sachdeva KS, Kshirsagar N, Parmar M, Ramachandran R, Padmapriyadarsini C, et al. Effectiveness and safety of bedaquiline under conditional access program for treatment of drug-resistant tuberculosis in India: An interim analysis. Indian J Tuberc. 2020;67(1):29-37.
[27] Cohen K, Maartens G. A safety evaluation of bedaquiline for the treatment of multi-drug resistant tuberculosis. Expert Opin Drug Saf. 2019;18(10):875-82.
[28] Full prescribing information Sirturotm (bedaquiline) Tablets. 2013. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204384s002lbl.pdf. [Accessed on: 2020 Aug 22].
[29] Field SK. Bedaquiline for the treatment of multidrug-resistant tuberculosis: Great promise or disappointment? Ther Adv Chronic Dis. 2015;6(4):170-84.
[30] Patel H, Pawara R, Pawara K, Ahmed F, Shirkhedkar A, Surana S. A structural insight of bedaquiline for the cardiotoxicity and hepatotoxicity. Tuberculosis (Edinb). 2019;117:79-84.
[31] Kaufman G. Adverse drug reactions: Classification, susceptibility and reporting. Nurs Stand. 2016;30(50):53-63.
[32] Guidelines for Use of Bedaquiline in RNTCP PMDT in India: Central TB Division. Available from: https://www.tbcindia.gov.in/index1.php?lang=1&level=2&sublinkid=4682&lid=3248. [Accessed on: 2020 Aug 22].
[33] Information NC for B, Pike USNL of M 8600 R, MD B, Usa 20894. "How-to" guide on the use of bedaquiline for MDR-TB treatment [Internet]. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. World Health Organization; 2014 [cited 2020 Aug 26]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK247434/.
[34] Bert V, Eline V, Tomas R, Joris V, Christophe G, Veerle F, et al. Which QT correction formulae to use for QT monitoring? Journal of the American Heart Association. 2016;5(6):e003264.
[35] The use of the WHO-UMC system for standardised case causality assessment [Internet]. [cited 2020 Aug 26]. Available from: http://www.WHO-UMC.org/graphics/4409.pdf.
[36] Diacon AH, Donald PR, Pym A, Grobusch M, Patientia RF, Mahanyele R, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: Long-term outcome, tolerability, and effect on emergence of drug resistance. Antimicrob Agents Chemother. 2012;56(6):3271-76.
[37] Tsuyuguchi K, Sasaki Y, Mitarai S, Kurosawa K, Saito Y, Koh T. Safety, efficacy, and pharmacokinetics of bedaquiline in Japanese patients with pulmonary multidrug-resistant tuberculosis: An interim analysis of an open-label, phase 2 study. Respir Investig. 2019;57(4):345-53.
[38] Diacon HA, Donald PR, Pym A, Grobusch M, Patienti a RF, Mahanyele R, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence. Am Soc Microbiol. 2012;56(6):3271-76.
[39] Tadolini M, Lingtsang RD, Tiberi S, Enwerem M, D'Ambrosio L, Sadutshang TD, et al. Cardiac safety of extensively drug-resistant tuberculosis regimens including bedaquiline, delamanid and clofazimine. Eur Respir J. 2016;48(5):1527-29.
[40] Guglielmetti L, Tiberi S, Burman M, Kunst H, Wejse C, Togonidze T, et al. QT prolongation and cardiac toxicity of new tuberculosis drugs in Europe: A Tuberculosis Network European Trialsgroup (TBnet) study. Eur Respir J. 2018;52(2):1800537
[41] Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: A systematic and critical analysis of the evidence. Eur Respir J. 2017;50(5):1701462.

PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Pharmacology, Burdwan Medical College, Burdwan, West Bengal, India.
2. Senior Resident, Department of Pharmacology, Burdwan Medical College, Burdwan, West Bengal, India.
3. Assistant Professor, Department of Pharmacology, Burdwan Medical College, Burdwan, West Bengal, India.
4. Associate Professor, Department of Respiratory Medicine, Burdwan Medical College, Burdwan, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Chitrita Ghosh,
Senior Resident, Department of Pharmacology, Burdwan Medical College, Baburbag, Burdwan, West Bengal, India.
E-mail: chitritaghosh@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 08, 2021
- Manual Googling: Nov 03, 2021
- iThenticate Software: Nov 19, 2021 (5%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 07, 2021**
Date of Peer Review: **Oct 12, 2021**
Date of Acceptance: **Nov 05, 2021**
Date of Publishing: **Feb 01, 2022**