Compassionate Use of Bedaquiline for the Treatment of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: Interim Analysis of a French Cohort

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Background. Bedaquiline is a new antibiotic that was approved for the treatment of multidrug-resistant (MDR) tuberculosis. We aimed to evaluate the short-term microbiological efficacy and the tolerability profile of bedaquiline.

Methods. We performed a retrospective cohort study among patients with MDR tuberculosis receiving bedaquiline for compassionate use between January 2010 and July 2013 and evaluated at 6 months of bedaquiline treatment.

Results. A total of 35 patients with MDR tuberculosis were included in the study. Nineteen (54%) had extensively drug-resistant (XDR) tuberculosis, and 14 (40%) had isolates resistant to fluoroquinolones (Fqs) or second-line injectables. Bedaquiline was associated with a median of 4 (range, 2–5) other drugs, including linezolid in 33 (94%) cases. At 6 months of bedaquiline treatment, culture conversion was achieved in 28 of 29 (97%) cases with culture-positive pulmonary tuberculosis at bedaquiline initiation. Median time to culture conversion was 85 days (range, 8–235 days). Variables independently associated with culture conversion were treatment with a Fq ($P = .01$), absence of lung cavities ($P < .001$), and absence of hepatitis C virus infection ($P = .001$). A total of 7 patients (20%) experienced a $\geq 60$-ms increase in QT interval, leading to bedaquiline discontinuation in 2 (6%) cases. Severe liver enzyme elevation occurred in 2 patients (6%). During the study period, 1 death (3%) occurred and was reported as unrelated to tuberculosis or antituberculosis treatment.

Conclusions. The use of bedaquiline combined with other active drugs has the potential to achieve high culture conversion rates in complicated MDR and XDR tuberculosis cases, with a reassuring safety profile at 6 months of treatment.

Keywords. TMC207; bedaquiline; safety; multidrug-resistant tuberculosis; extensively drug-resistant tuberculosis.

Despite recent achievements in reducing its global incidence, tuberculosis remains a major cause of death worldwide. The efforts to grant effective tuberculosis control have been impaired by the emergence of multidrug-resistant (MDR) strains and by the human immunodeficiency virus (HIV) epidemic. The World Health Organization estimated that approximately 450 000 new MDR tuberculosis cases, defined as resistant to isoniazid and rifampicin, occurred in 2012 [1]. In addition, extensively drug-resistant (XDR) tuberculosis, which is
defined as MDR tuberculosis with additional resistance to any fluoroquinolone (Fq) and at least 1 second-line injectable (2LI) antibiotic [2], has been estimated to account for almost 10% of all MDR cases in 2012 [1].

Dealing with MDR and XDR tuberculosis cases requires burdensome, poorly tolerated treatment regimens, which can last up to 24 months [3]. A large meta-analysis has shown an overall success rate of 54% in MDR tuberculosis patients [4]. When only subjects with available data on Fq and/or 2LI resistance were included, pooled treatment success rates for MDR and XDR tuberculosis cases were 64% and 40%, respectively [5].

In the last 12 months, 2 new molecules have been approved for the treatment of MDR tuberculosis: bedaquiline (Bdq) by the US Food and Drug Administration (FDA) and delamanid by the European Medicines Agency. Bedaquiline, developed as TMC207, belongs to a new class of antituberculosis drugs, the diarylquinolines, which inhibit the mycobacterial adenosine triphosphate synthase [6]. Bedaquiline has shown in vitro activity against both drug-sensitive and MDR Mycobacterium tuberculosis strains [7].

In the mouse model, Bdq was associated with an effective sterilizing activity [8, 9]. The combination of Bdq and pyrazinamide has been shown to have bactericidal and sterilizing efficacy [10–12].

A clinical trial (C208 study) comparing a second-line background regimen with or without 8 weeks of Bdq demonstrated a higher proportion of culture conversion at 6 months (81.0% vs 62.5%) in the Bdq arm [13, 14]. In the second stage of the study (C208-2), Bdq together with background regimen led to faster culture conversion and higher rates of culture conversion at 6 months of treatment than in the background regimen plus placebo arm [15]. Efficacy results in the open-label C209 study were consistent with those of the C208-2 trial [16]. Finally, pooled data from all studies conducted in humans showed a similar rate of mild-to-moderate adverse effects in Bdq and placebo-treated patients [16]. These promising results were counterbalanced by a worrying imbalance in the number of deaths found between the 2 treatment arms in the C208-2 trial, with 10 vs 2 deaths occurring in Bdq-treated patients [15].

The objective of our study is to evaluate the microbiological efficacy of Bdq-containing regimens, as well as the safety and tolerability profile of Bdq in patients treated under compassionate use in a MDR tuberculosis cohort in France, where a marked increase in the number of MDR tuberculosis cases has been observed since 2011 [17].

MATERIALS AND METHODS

The temporary authorization for use of Bdq was granted by the French National Agency for the Safety of Medicine and Health Products. The Bdq expanded-access use started in 2011. All MDR tuberculosis patients managed at the sanatorium of Bligny Hospital, in the Paris area, France, and treated by Bdq for at least 1 month between January 2011 and July 2013 were included in the retrospective analysis. Considering that Bdq administration is currently recommended for a maximum of 6 months [18], data for this interim analysis were collected for up to 6 months of Bdq treatment except for patients remaining culture or smear positive, who were followed until culture and smear conversion or until data censoring (February 2014).

Standard definitions were used for MDR and XDR tuberculosis. Bedaquiline was used as part of an individualized antituberculosis regimen, which was tailored to drug susceptibility testing (DST) results by a group of multidisciplinary experts (MDR Tuberculosis Management Group of the French National Reference Centre for Mycobacteria [NRC-MyRMA]), implemented after surveys on the MDR tuberculosis management in France [19, 20]. All drugs were administered as directly observed treatment during hospitalization. Bedaquiline was administered as recommended by the manufacturer: 400 mg once daily for 2 weeks, followed by 200 mg thrice weekly. Patients with pulmonary tuberculosis repeated smear and culture examinations every 2 weeks up to culture conversion, and monthly thereafter. Safety and tolerability of treatment were monitored through serial complete blood counts and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) measurements. An electrocardiogram was requested at baseline, and after 2, 4, 8, 12, and 24 weeks of Bdq treatment. QT interval was corrected for heart rate using Bazett formula (QTcB) [21]: corrected QT interval = QT/(RR interval)1/2. A prolongation of the QT interval was defined as ≥60 ms increase.

DST for first- and second-line drugs was conducted at the NRC-MyRMA by the proportion method on Löwenstein-Jensen medium [22].

Sputum smear and culture conversion were defined as 2 consecutive negative exams at least 2 weeks apart, in a patient with a positive specimen at baseline. Time to conversion was measured from the beginning of Bdq treatment to the time of the first of the 2 negative exams. Adverse events were considered as related to Bdq if that was the opinion of the treating physician.

Data were retrospectively extracted from medical records. Statistical analysis was performed using Stata software, version 11.1 (StataCorp). The $\chi^2$ test or Fisher exact test was used to compare categorical variables. Continuous variables were compared by the 2-sample Wilcoxon–Mann–Whitney test. Kaplan–Meier analysis was used to evaluate the time to smear and culture conversion. A Cox proportional hazards model with robust estimation of confidence interval (CI) was used to assess the association between time to culture conversion and explanatory variables. Variables associated with the time-to-event outcomes in univariate analysis ($P < .20$) were introduced into a multivariate model following a forward stepwise strategy. The test of the proportional hazards assumption and Cox-Snell
residuals were used to assess the model validity. Patients with missing information were censored at the date of the last available microbiological result. P values < .05 were considered statistically significant.

All patients included were treated according to Good Clinical Practice, and were informed about expected benefits and potential side effects of each drug including Bdq and its compassionate use, but were not asked to sign a consent form. Ethical approval was obtained from the institutional review board of the Bligny Hospital for the retrospective chart review.

RESULTS

Patient Characteristics

From 2010 to 2013, 35 patients with MDR tuberculosis received Bdq for at least 1 month. The median age was 39 years (range, 18–70 years), and 28 (80%) were male (Table 1). Most of them (n = 34 [97%]) were foreign-born. None were HIV-coinfected, 18 (51%) had hepatitis C virus (HCV) infection, and 8 (23%) had at least 1 more comorbid condition, mainly diabetes (5 patients [14%]) and renal failure (2 patients [6%]).

Disease Status on Admission

All patients but 1 (n = 34 [97%]) had pulmonary tuberculosis, including 5 (14%) with extrapulmonary involvement (2 genital tuberculosis, 1 osteoarticular and intra-abdominal tuberculosis, 1 myocardial tuberculosis, and 1 laryngeal tuberculosis). Among the 34 patients with pulmonary tuberculosis, 26 (77%) had bilateral lung involvement, and 29 (85%) at least 1 lung cavity and sputum-smear positivity at hospital admission (Table 2). The remaining patient had Pott disease.

A majority of patients (n = 24 [69%]) had a history of previous tuberculosis treatment, of whom 7 (20%) received only first-line drugs and 17 (49%) were treated with second-line drugs.

A total of 19 patients (54.3%) had XDR tuberculosis. Among the 16 (45.7%) others, 10 (28.6%) had isolates resistant to at least 1 Fq and 4 (11.4%) to at least 1 2LI. Two (5.7%) patients had strains susceptible to Fq and 2LI, but had medical contraindications to their use. Isolates were resistant to a median number of 9 drugs (range, 5–12), including pyrazinamide (n = 25 [71.4%]), ethambutol (n = 28 [80%]), streptomycin (n = 32 [91.4%]), ofloxacin (n = 29 [82.9%]), moxifloxacin (n = 21

Table 1. Demographic Characteristics of the 35 Patients With Multidrug-Resistant or Extensively Drug-Resistant Tuberculosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. (%) or Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Categorical variables</strong></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>28 (80)</td>
</tr>
<tr>
<td>Place of birth</td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>27 (77.1)</td>
</tr>
<tr>
<td>Africa</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Asia</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>France</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>HIV coinfected</td>
<td>0</td>
</tr>
<tr>
<td>HCV coinfected</td>
<td>18 (51.4)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>13 (37.4)</td>
</tr>
<tr>
<td>Presence of comorbidities</td>
<td>8 (23)</td>
</tr>
<tr>
<td><strong>Continuous variables</strong></td>
<td></td>
</tr>
<tr>
<td>Age at admission, y</td>
<td>39 (31–41)</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>32 (26.2–34.9)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>19.4 (17.4–22)</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range.
occurred after a median of 111 days of Bdq treatment.
mies, 2 bilobectomies, and 2 pneumonectomies), which
PAS (n = 26 [74.3%]), amikacin (n = 25 [71.4%]), imipenem
ionamide (n = 8 [22.9%]), and clofazimine (n = 5 [14.3%]). Of
ambutol (n = 11 [31.4%]), pyrazinamide (n = 10 [28.6%]), eth-
[65.7%]), cycloserine (n = 19 [54.3%]), Fq (n = 16 [45.7%]), eth-
combined with co-amoxiclav (amoxicillin/clavulanic acid; n = 23
– 171) prior to Bdq initiation.

Patients who received Bdq received a median of 4 additional antibiotics (range, 2–5), including linezolid (n = 33 [94.3%]), PAS (n = 26 [74.3%]), amikacin (n = 25 [71.4%]), imipenem combined with co-amoxiclav (amoxicillin/clavulanic acid; n = 23 [65.7%]), cycloserine (n = 19 [54.3%]), Fq (n = 16 [45.7%]), eth-
ambutol (n = 11 [31.4%]), pyrazinamide (n = 10 [28.6%]), eth-
ionamide (n = 8 [22.9%]), and clofazimine (n = 5 [14.3%]). Of
note, 31 (89%) received at least Fq or 2LI, including 15 XDR
ambutol (n = 11 [31.4%]). None were resistant to linezolid.

Nine (25.7%) patients had pulmonary surgery (5 lobecto-
mies, 2 bilobectomies, and 2 pneumonectomies), which
occurred after a median of 111 days of Bdq treatment.

Efficacy

Of the 29 patients with culture-positive pulmonary tuberculosis
at Bdq initiation, 21 (72%) achieved culture conversion after 3
months and 28 (97%) after 6 months of Bdq. At 3 and 6 months
of Bdq treatment, sputum-smear conversion occurred in 14
(48%) and 20 (69%) of the 29 initially smear-positive patients.
Median time to culture and sputum-smear conversion was 85
days (range, 8–235 days) and 103 days (range, 12–252 days),
respectively (Figure 1).

An Fq (ofloxacin or moxifloxacin)–containing regimen was
significantly associated with culture (P = .03) and sputum-
smear conversion (P = .02) after 3 months of treatment and
with a shorter time to culture conversion (P = .02). No similar
association was found with 2LI-containing regimens, nor with
the number of drugs with documented susceptibility at DST
and number of active compounds administered in association
with Bdq.

At 6 months of Bdq treatment, all patients but 1 had culture
conversion; this patient was infected by a MDR tuberculosis
strain that was resistant to both ofloxacin and moxifloxacin,
but maintained susceptibility to all 2LIs. In this case, culture
conversion was successively achieved after 235 days of Bdq
treatment.

In a multivariable Cox proportional hazards model (Table 3),
presence of lung cavities and HCV infection were associated
with a slower time to culture conversion (hazard ratio [HR],
0.04 [95% CI, .01–.20], P < .001 and HR, 0.21 [95% CI, .08–.54], P = .001, respectively), while treatment for ≥30 days
with any Fq was associated with a faster time to culture conver-
sion (HR, 3.28 [95% CI, 1.30–8.27], P = .01). After introduction
in the above model, treatment with imipenem/co-amoxiclav
was associated with a slower time to culture conversion (Table 3)
but was at the limit of statistical significance (P = .06). The other

Treatment

Bedaquiline was included in the initial MDR tuberculosis treat-
ment regimen for 26 (74.3%) patients, while 9 (25.7%) were
already treated for MDR tuberculosis for a median of 85 days
(range, 47–171) prior to Bdq initiation.

Figure 1. Kaplan–Meier analysis of time to smear and culture conversion of patients with positive smear and culture exams at the beginning of treatment with bedaquiline (N = 29). Median time to conversion is shown for both smear (solid vertical line) and culture (dashed vertical line). The vertical bar between 120 and 150 on the smear curve indicates censoring.
variables with \( P < .20 \) in univariate analysis (ie, treatment with pyrazinamide and bilateral lung involvement), did not reach statistical significance. The other factors were not tested in the multivariate model because they did not reach the \( P \) level of \(<.20\) in univariate analysis.

**Safety and Tolerability**

Mean QT\(_{cB}\) values increased by a median of 1.96 ms (range, \(-64\) to 71 ms) during Bdq treatment. The increase was greater, although not statistically significant, in patients receiving Bdq combined with Fq (median, 4.9 ms) or clofazimine (median, 7.3 ms) than in those not treated with any of these 2 QT-prolonging drug classes (median, \(-5.3\) ms).

Overall, 7 (20%) patients had an increase of QT\(_{cB}\) ≥60 ms from baseline and 3 (9%) had a QT\(_{cB}\) value >500 ms. None of these events was found to be significantly associated with Fq or clofazimine administration. Bedaquiline was discontinued in 2 (6%) patients due to persistent QT\(_{cB}\) prolongation: 1 receiving moxifloxacin, and the other clofazimine and amiodarone. No cardiac arrhythmia was recorded.

Mild liver enzyme elevation (\(≥2\)-fold baseline) was reported in 5 (14%) patients, and \(≥5\)-fold increase occurred in 2 additional patients (6%). In the latter, elevation was confounded by the concomitant intake of hepatotoxic compounds (pyrazinamide, Fq, PAS). Liver enzymes elevations were asymptomatic and did not lead to Bdq discontinuation. In both patients, AST and ALT levels peaked after 3 months of Bdq treatment and reverted to normality during the subsequent month. In 1 case, treatment with PAS was suspended following liver enzyme elevation.

One death occurred during the surveillance period, in a patient affected by an advanced pharyngolaryngeal cancer, who received Bdq for 31 days and subsequently stopped, following QT\(_{cB}\) prolongation. Early culture and sputum-smear conversion were achieved and death occurred 4 months after Bdq discontinuation and 9 months after starting active antituberculosis therapy. Therefore, death was considered to be related to the malignancy.

One patient had coronary artery dissection during percutaneous coronary stenting. No other clinically relevant adverse events were associated with Bdq use, and the total number of non-Bdq-related adverse events was 80.

**DISCUSSION**

Following the recent “fast-track” approval of Bdq by the FDA, it is crucial to increase the amount of clinical evidence on this compound. The aim of this interim analysis at 6 months of treatment was to assess data on Bdq efficacy and tolerability in a cohort of patients treated for MDR and XDR tuberculosis.

Our results show that Bdq-containing regimens used in accordance with provisional guidelines [18, 23] led to a high rate (97%) of culture conversion after 6 months for these difficult-to-treat patients. Faster culture conversion was associated with Fq-containing regimens, whereas lung cavities and HCV infection were associated with slower time to conversion. Treatment was overall well tolerated, despite the fact that QT\(_{cB}\) prolongation was fairly common.

In our study, the culture conversion rate was 97% after 6 months of Bdq. This is higher than in the randomized trials performed so far [14–16]. Of interest, Bdq was combined with linezolid in 94% of our patients. The relevant role of linezolid in the treatment of MDR tuberculosis and particularly of Fq-resistant strains has been recently highlighted and could partially explain our satisfactory results [24]. Indeed, a culture conversion rate of 87% has been reported in MDR tuberculosis patients treated with linezolid [25]. Of note, the proportion of XDR patients in the latter study and in most linezolid-treated cohorts is around 10% [25–27]. In a Portuguese MDR tuberculosis cohort with a high rate of XDR tuberculosis treated with linezolid, only 57% of subjects achieved culture conversion at 6 months [28]. In our cohort, 66% of the patients received a carbapenem and co-amoxiclav. This combination with linezolid-containing regimens has also shown promising preliminary results [26]. The fact that 89% of our patients received either Fq or 2LI must be taken into account as well when evaluating the results observed in our cohort. Indeed, the major role of the latter drug classes, and especially Fq, has already been emphasized [5, 29–32]. This is reinforced by the fact that Fq use was the only factor independently associated with faster culture conversion in our study. This finding suggests that Bdq cannot replace the fast bactericidal activity of Fq. This is consistent with previous early bactericidal activity studies [33]. In contrast with existing data [9, 10, 34], pyrazinamide combined with Bdq had no effect on culture conversion in our study. This finding may be related to the reduced number of patients harboring pyrazinamide-susceptible strains. Moreover, the synergistic sterilizing effect of the Bdq/pyrazinamide combination on the prevention of relapses is to be appreciated during the follow-up after treatment end.

In our cohort, longer time to culture conversion was associated with the presence of lung cavitations and to HCV infection. Although lung cavitations are well-known risk factors for treatment failure [31, 35], HCV infection has only been associated with an increased risk of hepatitis during tuberculosis therapy [36] but not with poor treatment outcomes [37].

Side effects were rather common in our study, which is typically the case in MDR tuberculosis treatment. Bdq-associated adverse events were mostly mild or moderate and regressed spontaneously. The proportion of patients who experienced a ≥60-ms QT\(_{cB}\) increase during treatment (20%) was higher than in previous studies and, as found in the C209 trial, more
pronounced in patients receiving Bdq in association with clofazimine [16]. Of note, QTcB values >500 ms were also more frequent in our study (9%) and led to Bdq discontinuation in 2 patients. However, as previously reported, no arrhythmias occurred. The incidence of liver enzyme elevation (14%) was fairly comparable to previous trials, with severe (≥5-fold) increase reported in only 6% of patients [16].

In our study, the only death was recorded in a patient with a severe underlying disease. It occurred following a surgical intervention, several months after having stopped Bdq, and was not associated with >500-ms QTcB values.

This study has several limitations, which derive mostly from its observational nature. The choice of evaluating the 6-month rate of culture conversion and the time to culture conversion as surrogate markers of treatment outcomes was justified by the purpose of our interim analysis. Treatment outcome data are not yet available. As late failure or relapse is a major problem in MDR tuberculosis treatment, our interim results should be interpreted with caution. The evaluation of the individual role of Bdq in treatment efficacy and safety is also limited by the use of a heterogeneous array of accompanying drugs as part of individualized treatment regimens. In addition, we did not compare our results in the Bdq cohort to a control arm. However, in our cohort with a large number of XDR tuberculosis, very few alternatives to Bdq were available. Finally, QT interval was corrected for heart rate using the Bazett instead of the Fridericia formula, which is recommended by the Bdq manufacturer. The Bazett formula is less accurate at higher and lower heart rates, but it is arguably the most widely used correction and better reflects the daily clinical practice.

In conclusion, this study suggests that Bdq combined with other active drugs has the potential to achieve high culture conversion rates in cases of advanced MDR and XDR tuberculosis with additional resistance to multiple first- and second-line antituberculosis drugs. Although short-term safety data seem reassuring, it is crucial to follow carefully all patients for severe adverse events even after Bdq discontinuation. This is of major importance in the prospect of the combination of Bdq with other innovative antituberculosis drugs [38].

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


**APPENDIX**


*Members of the Physicians of the French MDR-TB Cohort.*