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Bedaquiline for the Treatment of Multidrug-resistant Tuberculosis in the United States

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Abstract

Background—In 2012, the Food and Drug Administration approved use of bedaquiline fumarate as part of combination therapy for multidrug-resistant tuberculosis (MDR TB). We describe treatment outcomes, safety, and tolerability of bedaquiline in our case series.

Methods—Data on patients started on bedaquiline for MDR TB between September 2012 and August 2016 were collected retrospectively through 4 TB programs using a standardized abstraction tool. Data were analyzed using univariate methods. Adverse events were graded using the Common Terminology Criteria for Adverse Events.

Results—Of 14 patients, 7 (50%) had MDR, 4 (29%) had pre-extensively drug-resistant (XDR), and 3 (21%) had XDR TB. All had pulmonary TB, 5 (36%) had pulmonary and extrapulmonary TB, and 9/13 (69%) were smear positive. One patient (7%) had HIV coinfection, 5 (36%) had diabetes mellitus, and 5/14 (36%) had previous treatment TB. All patients were non-US-born and 5/14 (36%) had private insurance. All patients achieved sputum culture conversion within a mean of 71 days (26–116); 5 after starting bedaquiline. Twelve (86%) completed treatment and 1 (7%) moved out of the country. One patient (7%) had QTc prolongation >500 milliseconds and died 20 months after discontinuing bedaquiline of a cause not attributable to the drug. Common adverse

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

events were peripheral neuropathy 7/14 (50%), not customarily associated with bedaquiline use, and QTc prolongation 6/14 (43%).

Conclusions—Of 14 patients, 1 (7%) had an adverse event necessitating bedaquiline discontinuation. Safety, culture conversion, and treatment completion in this series (7%) support use of bedaquiline for the treatment of MDR/XDR TB.

Keywords

multidrug-resistant tuberculosis; bedaquiline; treatment; adverse event; outcome

Multidrug-resistant tuberculosis (MDR TB), defined as TB with an isolate resistant to at least isoniazid (INH) and rifampin (RIF), and extensively drug-resistant TB (XDR TB), defined as MDR TB with additional resistance to a fluoroquinolone and an injectable agent, threaten communities around the world and pose a global public health emergency that needs to be addressed. Drivers of drug-resistant (DR) TB include inadequate treatment regimens due to lack of provider knowledge, compounded by limited access to new, quality-assured, well-tolerated medications and timely drug susceptibility testing and the inability to complete treatment due to toxic, lengthy, and expensive treatment regimens. Globalization and the lack of infection control measures further amplify the problem due to transmission of DR TB strains from person to person [1, 2].

With the advent of rapid molecular tests for detection of rifamycin-resistant (RR) strains, the numbers of detected cases of MDR/RR TB are on the rise worldwide [3, 4]. The recently published Global TB Report 2018 [5] states that an estimated 3.5% of new cases and 18% of previously treated cases had MDR/RR TB in 2017. There were an estimated 558 000 incident cases of MDR/RR TB in 2017 and, by the end of 2017, XDR TB had been reported by 127 countries. The average proportion of MDR TB cases with XDR TB was 8.5%, an increase from 6.2% reported from 2016. Although the number of TB cases have declined steadily in the United States since 1993 (2017 case count, 9105), the proportion of MDR TB has remained relatively constant between 1% to 2%. In 2017 in the United States, the proportion of MDR TB was 1.6% and 2 cases of XDR TB were reported [6].

With an increase in MDR/RR TB case detection and the emergence of pre-XDR TB (MDR TB with additional resistance to either a fluoroquinolone or an injectable agent) and XDR TB, it is important to initiate and complete treatment for all diagnosed patients. Newer, better tolerated, and shorter treatment regimens are essential for addressing the global epidemic of DR TB adequately. The World Health Organization (WHO) has recently provided guidance for 2 new drugs, bedaquiline fumarate and delamanid, and made recommendations for the use of a shorter MDR TB regimen of 9–12 months' duration [7–10]; the most recent update to the WHO guidelines [11] recommends the use of bedaquiline as an initial drug in an all-oral regimen designed to maximize treatment outcomes and minimize toxicity associated with injectable agents. These guidelines are based on an individual patient data meta-analysis [12] and operational data from countries' experience with the use of bedaquiline [13]. Countries are in different stages of implementation of these new treatment strategies. Delamanid has not been upgraded in the WHO recommendations

or approved for use in the United States, although it has been approved for use in the European Union [14].

Phase II clinical trial data showed that bedaquiline was effective based on culture conversion when compared with placebo, but that safety might be an issue because of increased all-cause mortality in the bedaquiline arm [15, 16]. Based on these data, in December 2012, the US Food and Drug Administration (FDA) approved bedaquiline fumarate, an oral diarylquinoline with a novel mechanism of action against *Mycobacterium tuberculosis* (inhibition of ATP synthetase), and the first drug in a new class of anti-TB medications in over 40 years. The approval was made under the provisions of accelerated approval regulations for "Serious or Life-Threatening Illnesses" (21 CFR 314.500) and included a recommendation to capture data on effectiveness and safety of the drug in US patients due to the paucity of data and increased all-cause mortality found in the bedaquiline arm of the phase II trial [15, 16]. Bedaquiline was approved to be "used with expert consultation, as part of combination therapy and administered by direct observation, to adults (≥18 years) with a confirmed diagnosis of pulmonary MDR TB" [17].

Centers for Disease Control and Prevention (CDC) guidelines for the use of and safety monitoring of bedaquiline in persons diagnosed with MDR TB in the United States were published in October 2013 and addressed specific safety concerns, especially the potential for bedaquiline to cause QTc prolongation (increase of 60 ms from baseline or QTc >500 ms), increasing the risk of Torsades de Pointes, a polymorphic ventricular tachycardia that can degenerate into ventricular fibrillation [18]. The guidelines recommend that patients started on bedaquiline have electrocardiogram (ECG) monitoring at baseline and at 2, 12, and 24 weeks after starting treatment; monitoring of electrolytes (calcium, magnesium, and potassium) at baseline and if QTc prolongation is noted; and enhanced weekly ECG monitoring if receiving other QTc-prolonging drugs, other risk factors for arrythmias are present, or if electrolytes are found to be abnormal. Furthermore, it is recommended that bedaquiline be discontinued if a clinically significant ventricular arrythmia occurs or if QTc greater than 500 ms is noted on 2 sequential ECGs. Most patients who met criteria through August 2016 per CDC guidelines were started on bedaquiline as part of a multidrug regimen [18]. We describe treatment outcomes and adverse events (AEs) of a case series of patients in the United States with MDR/XDR TB who have been treated with bedaquiline and report on the implementation of this new drug for the treatment of MDR/XDR TB.

METHODS

The CDC established a voluntary registry and standardized monitoring system to track outcomes of patients started on bedaquiline for MDR TB, including AEs, laboratory data, and other pertinent variables. Twenty-one patients who started on bedaquiline between September 2012 (1 patient received bedaquiline through the Janssen Foundation compassionate-use program prior to FDA approval) and August 2016 were identified through the registry, CDC-funded Regional Training and Medical Consultation Centers (RTMCCs), and state TB programs. Data were collected on 14 patients through 4 sites using a standardized abstraction tool, entered into an Excel spreadsheet (Microsoft Corporation), and analyzed using univariate methods; data on the other 7 patients were

not obtained due to resource or programmatic constraints. For additional methods, definitions, and ethical review, see the Supplementary Material.

RESULTS

Our 14-patient case series includes patients who received bedaquiline as part of a multidrug regimen for MDR TB during the time frame for this study. Of these, 7 of 14 (50%) had MDR, 4 of 14 (29%) had pre-XDR, and 3 of 14 (21%) had XDR TB. All had culture-positive pulmonary TB, 5 of 14 (36%) had both pulmonary and extrapulmonary TB, and 9 of 13 (69%) were acid-fast smear positive. Of the 14, 12 (86%) had an abnormal chest radiograph, and of these 12, 7 (58%) had cavitary disease. One of the 14 (7%) had human immunodeficiency virus (HIV) coinfection and 5 of 14 (36%) had diabetes mellitus (Tables 1 and 2).

All patients were non-US born and 5 of 14 (36%) had been previously treated. The Philippines was the most common country of birth (21%), followed by India, China, Armenia (each 14%), and finally, Peru, Nigeria, and Uzbekistan (each 7%) (Table 2). Bedaquiline was paid for by private insurance for 5 of 14 (36%) patients, by state or local health departments for 5 of 14 (36%) patients, by a government plan for 2 of 14 (14%) patients, and 2 of 14 patients (14%) had other sources of payment (eg, Janssen Foundation compassionate-use program) (Tables 1 and 2).

Indications for bedaquiline use were extensive resistance for 8 of 14 patients (57%), intolerance to medications for 6 of 14 patients (43%), poor clinical response to treatment for 2 of 14 patients (21%), and treatment failure for 1 patient (7%). The mean number of effective drugs in the regimen during the intensive phase was 7 (range, 5–9) and 5 (range, 4–6) during the continuation phase. The median time on treatment before bedaquiline was started was 94 days (interquartile range [IQR], 37–443 days), the median duration of treatment with bedaquiline was 173 days (IQR, 165–193 days), and the total median MDR TB treatment was 742 days (IQR, 687–858.5 days). All patients achieved culture conversion with median time-to-culture conversion being 71 days (IQR, 26–116 days); however, bedaquiline was only started prior to culture conversion for 8 of 14 (57%) patients. Twelve (86%) completed treatment, 1 of 14 (7%) patients moved, and 1 of 14 (7%) patients discontinued bedaquiline treatment due to a QTc interval greater than 500 ms and died at an age older than 80 years of a cerebral event 20 months after stopping bedaquiline (Tables 1 and 2).

Resistance to first-line anti-TB drugs was high in isolates, with 13 of 14 (93%) isolates resistant to ethambutol (EMB) and 10 of 14 (71%) isolates resistant to pyrazinamide (PZA). Of 13 isolates tested for streptomycin (SM) susceptibility, 9 (69%) were resistant, and of 12 isolates tested for rifabutin susceptibility, 8 (67%) were resistant. Among second-line drugs, there was greatest resistance to ethionamide (ETA), with 9 of 14 (69%) that were resistant, followed by fluoroquinolones with 5 of 13 (38%) that were resistant to ciprofloxacin and 5 of 12 (42%) that were resistant to ofloxacin. Second-line injectable resistance was lower, with 3 of 13 (23%) isolates resistant to kanamycin, 1 of 14 (7%) resistant to capreomycin, and 2 of 14 (14%) resistant to amikacin. Other second-line drug resistance was low, with 2

of 14 (14%) isolates resistant to para-amino salicylic acid (PAS), 1 of 7 (14%) resistant to clofazimine (CFZ), and no resistance detected in 10 patients who had cycloserine susceptibility testing and 8 patients who had susceptibility testing to linezolid. One patient acquired resistance to PZA during treatment. Five patients had 1 or more discrepant susceptibility results to the following drugs: EMB, PAS, ETA, injectable agents, or moxifloxacin (MFX) (Table 3).

Grade 2 and 3 AEs of peripheral neuropathy (50%) and QTc prolongation (43%) were the most common AEs (Table 4). All patients with an AE of peripheral neuropathy were taking linezolid. Among the 6 patients with QTc prolongation, all were taking 1 or more other QTc-prolonging drugs, 5 of 6 (83%) had an increase of 60 ms from baseline, and 4 of 6 (67%) had a QTc greater than 500 ms. Patients 1 and 4 did not have a QTc greater than 500 ms and therefore had no change in treatment regimen, and patient 11 was found to have a QTc of 432 ms on an ECG performed the next day and therefore had no change in treatment regimen. Patient 12 was found to have hypokalemia and bedaquiline was stopped and restarted within 2 weeks once the hypokalemia was corrected. Patient 14 was found to have a QTc of 546 ms 1 day after bedaquiline treatment was completed, which was corrected by stopping MFX and CFZ. Patient 3 had bedaquiline discontinued due to a QTc of 507 ms. In summary, of the patients with a QTc greater than 500 ms, 3 of 4 (75%) completed a full course of bedaquiline and 1 of 4 (25%) discontinued and did not restart bedaquiline (Table 5). Other AEs included electrolyte disturbances in 4 of 14 patients (29%), gastrointestinal intolerance in 4 of 14 patients (29%), psychiatric disturbances in 3 of 14 patients (21%), dermatologic reactions in 3 of 14 patients (21%), hearing loss in 2 of 14 patients (14%), and anemia in 2 of 14 patients (14%). There were no deaths while taking bedaquiline (Table 4).

DISCUSSION

This is the first report of outcomes, tolerability, and AEs among patients taking bedaquiline for TB in the United States. Although the United States was the first country to approve its use, uptake and implementation of the drug have been limited due to small numbers of patients with sufficient drug resistance for whom use of this drug would be indicated per FDA labeling. In the past 5 years, there have been 80 to 100 incident MDR TB cases reported annually in the United States [6]. All patients who received bedaquiline for the indication of MDR TB met strict FDA criteria for its use and, despite the small numbers, the results of treatment with a multidrug regimen including bedaquiline for MDR/XDR TB have been promising and mirror the experience published from different settings globally [19–21]. The numbers of patients receiving bedaquiline may increase with the new WHO DR TB guidelines that recommend an all-oral bedaquiline-containing regimen for most patients with MDR TB [11]. Bedaquiline is also increasingly being considered on an “off label” basis for treatment of disease caused by nontuberculous mycobacteria, and more patients have received bedaquiline for this indication in the United States than for MDR TB.

Of 14 patients with complex MDR/XDR TB in this series, all achieved culture conversion and all completed treatment except for 1 patient who moved and 1 death. There were no reported serious AEs ascribed to the use of bedaquiline, and putative AEs were few and potentially attributable to other supporting drugs in the regimen. QTc interval prolongation

was the key AE likely associated with bedaquiline use. Half of the patients had significant QT interval prolongation, and this resulted in treatment discontinuation in 1 patient. The 1 death that occurred in a patient older than 80 years was not thought to be attributable to bedaquiline.

Treatment success rates for MDR/XDR TB are quite good in the United States. In a study by Marks et al [22] assessing outcomes of 135 patients with MDR and XDR TB treated at 3 different sites in the United States during 2005–2007, 78% completed treatment, 11% moved and were lost to follow-up, 9% died (75% due to TB), and 1% stopped treatment due to AEs. Our results mirror these with a high treatment completion, despite substantially greater drug resistance observed in our case series providing the indication for use of bedaquiline. The future use of bedaquiline at treatment initiation and as part of an all-oral regimen may preserve the good overall treatment outcomes while improving time to culture conversion and minimizing AEs, such as hearing loss associated with the injectable agents.

All of the patients in this series were non-US born compared with 87% of those in the study published by Marks et al [22]; this might be explained by the changing demographics of TB in general and DR TB specifically in the United States, with more disease occurring in non-US-born persons over time [6]. It might also be explained by the fact that all patients in our analysis were receiving bedaquiline, and greater drug resistance has been associated with both bedaquiline use and non-US-born status. The percentage of previously treated patients was 36% in the Marks et al study [22] and 36% in our case series, suggesting that acquired drug resistance is the less common etiology of MDR/XDR TB in the United States. This is ominous as two-thirds of patients in both studies, having no history of prior treatment, likely acquired MDR/XDR TB infection through person-to-person transmission, underlining the need for rapid diagnosis of disease and of drug susceptibility, effective treatment, and infection control.

Comorbidities, such as HIV and diabetes mellitus, were present and slightly but not significantly different in prevalence between the Marks et al study [22] and this series. In the Marks et al study [22], 85% of patients had pulmonary disease, 6% extrapulmonary only, and 9% disseminated TB. In our study, all patients had pulmonary disease, with 36% also having extrapulmonary disease. This may reflect improved diagnosis of extrapulmonary TB over time as patients included in this study were diagnosed 7 to 10 years later than those in the Marks et al study [22].

Similar to our series, AEs were common in the Marks et al study [22] and only led to treatment discontinuation in 1% of patients (1 patient in our study). The 14% occurrence of hearing loss in this analysis was similar to the Marks et al study [22], which observed 13%, but quantification of other potential AEs was difficult to compare given differences in regimens. As global recommendations shift toward an all-oral bedaquiline-containing regimen, auditory, vestibular, and renal toxicity from the injectable agents will be eliminated [11].

The cost of treatment of patients with MDR/XDR TB thus far in the United States has been largely borne by the public sector, with very few patients having private insurance [22]. The

mechanism for payment for these patients has been haphazard, with some patients and TB programs having to go through the lengthy process of devising a fiscal plan for financing treatment. Furthermore, the current cost of the 6-month course of bedaquiline ($30 000) and distribution by a sole source may serve as barriers to access. Outside of the United States, US governmental entities such as the US Agency for International Development pay for much of the bedaquiline that is used worldwide. Systematic approaches for paying for these patients with complicated, drug-resistant TB within the United States are needed. A lengthy process of drug procurement can lead to delays in treatment, poor patient outcomes, and further transmission of MDR/XDR TB.

All patients in this series had access to expert consultation through CDC-funded regional consultation centers and state or local health departments. To ensure expert consultation was obtained, CDC put in place a systematic process for bedaquiline procurement and distribution that strongly recommended consultation from physicians trained in treating MDR TB. This was based on data that patients with MDR TB have better outcomes with expert clinical consultation [23]. This systematic process also ensured that, in treatment of TB, only patients who met criteria per CDC guidelines for bedaquiline [18] use received the drug in the public health sector linked to expert clinical consultation; the intent was to minimize the potential for AEs, for acquired drug resistance, and for poor patient outcomes due to inadequate treatment practices.

This report has several limitations. No post-treatment data were collected, limiting the ability to capture TB relapse or recurrence. Additionally, although the registry intended to collect data on all patients with TB receiving bedaquiline, data were not collected on a subset of patients because of human subjects ethics approval considerations and lack of funding for a sophisticated real-time surveillance system. Therefore, the patients in this study may not be representative of all patients with TB who received bedaquiline in the United States. The number of patients included in this report is small and, therefore, the data are not robust enough to draw significant conclusions on the effectiveness of bedaquiline for the treatment of MDR TB. However, a new MDR TB supplemental surveillance system has been proposed as part of the revision to the US TB surveillance system in 2020 [24]. This new system would provide data on treatment regimens and AEs for all patients in the United States with MDR TB.

Conclusions

In this case series of patients with TB receiving bedaquiline in the United States, culture conversion and treatment success rates were high despite extensive resistance. This group had low mortality compared with published outcomes of patients with pre-XDR and XDR TB [25, 26], and there were no documented serious AEs ascribed to bedaquiline. Our data suggest that bedaquiline is well tolerated with few significant AEs and effective in a multidrug regimen based on treatment success rates. Bedaquiline use can be implemented successfully in US TB programs if financial and procurement barriers can be addressed to ensure its availability for all patients who could benefit. The new WHO DR TB guideline recommending bedaquiline as an initial core drug for MDR TB [11] will ensure that more patients with MDR TB can benefit from this drug; these results offer support for that

recommendation. Last, a fully funded, real-time, AE monitoring and surveillance system is needed (the anticipated MDR TB supplemental surveillance system may fulfill this role) for collecting data more effectively and efficiently on patients receiving new drugs and regimens to ensure best practices for the care and treatment of patients with MDR/XDR TB.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of Patients Treated With Bedaquiline

Patient Characteristics	No. (%) or Median (IQR)
Age, years	43.5 (36.5–48.5)
Male sex	10 (71)
Previous TB treatment, yes	5 (36)
Positive HIV status	1 (7)
Diabetes, yes	5 (36)
Site of disease	
Pulmonary	14 (100)
Both pulmonary and extrapulmonary	5 (36)
Sputum smear positive[a]	9 (69)
Sputum culture positive	14 (100)
CXR, abnormal	12 (86)
Cavitary	7 (58)
Drug-resistance profile	
MDR	3 (21)
Resistance to INH, RIF, EMB, PZA (AFLDR)	4 (29)
Pre-XDR (FQN-resistant)	4 (29)
XDR	3 (21)
Number of effective drugs in regimen	
Intensive phase[b]	7 (5–9)
Continuation phase[c]	5 (4–6)
Duration of MDR therapy, days	768 (687–858.5)
Time on therapy before BDQ start, days	94 (37–443)
Indication for BDQ	
Extensive resistance	8 (57)
Rx failure	1 (7)
Intolerance to drugs	6 (43)
Poor clinical response to treatment	2 (14)
Duration of BDQ use, days	173 (165–193)
Payment for BDQ	
Private insurance	5 (36)
Government plan	2 (14)
State/local HD	5 (36)
Other	2 (14)
Time to culture conversion, days	71 (26–116)
Treatment outcomes	
Completed	12 (86)
Moved out of country	1 (7)
Died on treatment	1 (7)

N = 14.

Abbreviations: AFLDR, all first-line drug resistant; BDQ, bedaquiline; CXR, chest X-ray; EMB, ethambutol; FQN, fluoroquinolone; HD, health department; HIV, human immunodeficiency virus; INH, isoniazid; IQR, interquartile range; MDR, multidrug-resistant; PZA, pyrazinamide; RIF, rifampin; XDR, extensively drug-resistant; TB, tuberculosis.

[a] One smear not done. Denominator out of 13.

[b] Intensive-phase effective drugs: number of drugs in treatment regimen the patient was sensitive to or otherwise determined effective, while taking any injectable.

[c] Continuation-phase effective drugs: number of drugs in treatment regimen the patient was sensitive to or otherwise determined effective, after injectables had been discontinued.

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Table 2.

Demographic and Clinical Features of the Patients

Patient	Age at Diagnosis, years	Country of Birth	Smear	Time to CC, days	CXR	Drug-resistance Profile	Duration of MDR Therapy, days	Time on Therapy Before BDQ, days	Indication for BDQ	Duration of BDQ Use, days	Tx Outcome
1	20–40	India	Neg	36	Normal	Pre-XDR	553	4	Extensive resistance	186	Completed
2	40–60	Nigeria	Pos	42	Cavitary	AFLDR[a]	591	57	Extensive resistance	187	Completed
3[b]	>80	Mexico	Pos	101	Abnormal	AFLDR	705	2	Extensive resistance	86	Died
4	60–80	Mexico	Pos	149	Cavitary	MDR	804	523	Extensive resistance/ intolerance to drugs	165	Completed
5	20–40	Armenia	Pos	149	Cavitary	XDR	869	525	Extensive resistance/ intolerance to drugs	195	Completed
6	20–40	India	Neg	27	Normal	MDR	924	730	Intolerance to drugs	179	Completed
7	40–60	China	Not done	616	Cavitary	Pre-XDR	1294	620	Treatment failure/poor clinical response to treatment	166	Completed
8	20–40	Peru	Pos	140	Cavitary	XDR	n/a	0	Extensive resistance	365	Moved
9	20–40	Uzbekistan	Neg	60	Abnormal	Pre-XDR	443	31	Extensive resistance	158	Completed
10	40–60	China	Pos	50	Abnormal	Pre-XDR	732	56	Extensive resistance	167	Completed
11	20–40	Armenia	Pos	110	Cavitary	XDR	827	68	Poor clinical response to treatment	596	Completed
12	40–60	Philippines	Pos	222	Abnormal	MDR	681	203	Intolerance to drugs	153	Completed
13	40–60	Philippines	Neg	60	Cavitary	AFLDR	662	195	Intolerance to drugs	223	Completed
14	40–60	Philippines	Pos	28	Abnormal	AFLDR	559	120	Intolerance to drugs	167	Completed

N = 14.

Abbreviations: AFLDR, all first-line drug resistant; BDQ, bedaquiline; CC, culture conversion; CXR, chest X-ray; EMB, ethambutol; INH, isoniazid; MDR, multidrug-resistant; n/a, not applicable; Neg, negative; Pos, positive; PZA, pyrazinamide; RIF, rifampin; XDR, extensively drug-resistant; Tx, treatment.

[a]Resistance to INH, RIF, EMB, PZA.

[b]Patient 3 died secondary to cerebral degeneration but completed nearly 2 years of treatment.

Table 3.

Drug Susceptibility Results of Patients

Patient No.	BDQ[a]	INH	RIF	PZA	EMB	SM	ETA	KM	CS	CM	PAS	AK	RFB	CIP	OFLOX	MFX	CFZ	LFX	AMX-CLV	LZD	Molecular Detection Results
1	...	R	R	R	R	R	S	S	S	S	S	S	...	R	R	R	S	R	...	S	...
2	...	R	R	R	R	R	S	S	S	S	S	S	S	S	S	...	...	...	...	S	...
3	...	R	R	R	R	S	R	S	S	S	S	S	R	S	S	...	S	...	...	...	rpoB, gyrA, rrs
4	...	R	R	S	S	R	R	S		S	R	S	R	S	S	...	...	...	...	...	...
5	...	R	R	S	R	R	S	R	S	S	S	S	R	R	R	R	S	R	R	S	katG, rpoB
6	S	R	R	S	R	R	S	S	S	S	S	S	R	S	S	...	S	...	...	S	katG, rpoB, embB, rpsL
7	...	R	R	S	R	R	S	S	S	S	R[b]	S	R	S	S	R	...	S	...	...	embB
8	...	R	R	R	R	R	R[b]	R	S	S[b]	S	R	R	R	R	R	S	R	...	S	katG, rpoB, embB, pncA, gyrA, rrs
9	...	R	R	R	R	R	R	S	S	S	S	S	R	R	R	R[a]	S	R	...	S	inhA, katG, mabA, rpoB, embB, pncA, gyrA
10	...	R	R	R	R	...	R	...	S	S	S	S	...	...	...	R	...	...	...	S	katG, rpoB, embB, pncA, gyrA
11	S	R	R	R	R	R	R[b]	R[b]	S	R	S[b]	R[b]	R	R	R	R	R	...	...	S	katG, rpoB, gyrA, embB, pncA, eis
12	...	R	R	S	R[b]	S	R[b]	S	...	S	S	S	S	S	S	S	...	...	...	...	inhA, rpoB
13	S	R	R	R	R	S	R	S	...	S	S	S	S	S	S	...	...	...	...	...	inhA, rpoB
14	...	R	R	R	R	S	R	S	...	S	S	S	S	S	S	S	...	...	...	...	rpoB
Total number resistant	...	14/14 R	14/14 R	9/14 R	13/14 R	9/13 R	9/14 R	3/13 R	0/10 R	1/14 R	2/14 R	2/14 R	8/12 R	5/13 R	5/12 R	7/9 R	1/7 R	4/4 R	1/1 R	0/8 R	

Abbreviations: AK, amikacin; AMX-CLV, amoxicillin-clavulanate; BDQ, beclaquiline; CFZ, clofazimine; CIP, ciprofloxacin; CM, capreomycin; CS, cycloserine; EMB, ethambutol; ETA, ethionamide; INH, isoniazid; KM, kanamycin; LFX, levofloxacin; LZD, linezolid; MFX, moxifloxacin; OFLOX, ofloxacin; PAS, para-aminosalicylic acid; PZA, pyrazinamide; R, resistant; RFB, rifabutin; RIF, rifampin; S, susceptible; SM, streptomycin.

[a] BDQ susceptibility performed by Janssen Pharmaceuticals.

[b] Discrepant drug susceptibility testing results.

Table 4.

Adverse Events While on BDQ Treatment in Multidrug Regimen

Adverse Event	Rate of Prevalence, no. (%)
Neuropathy	7 (50)
QTc abnormalities	6 (43)
QTc increase 60 ms from baseline	5 (83)
QTc ≥500 ms	4 (67)
K+ abnormalities	4 (29)
Hyperkalemia	1 (25)
Hypokalemia	2 (50)
Both	1 (25)
GI disturbances	4 (29)
Psychiatric disturbances	3 (21)
Dermatologic reaction	3 (21)
Hearing loss	2 (14)
Anemia	2 (14)
Other[a]	3 (21)

N = 14.

Abbreviations: BDQ, bedaquiline; GI, gastrointestinal; K+, potassium.

[a]"Other" identifies instances of only 1 side effect, including acute kidney injury, decreased appetite, fatigue, arthralgia, and drug reaction. There were only 3 individuals between these 5 side effects.

Table 5.

QTc Abnormalities and Medical Outcomes

Patient No.	QTc Baseline	QTc Peak	Concurrent QTc-Prolonging Drugs	Medical Response	Finished Course of Bedaquiline?
1	384	469	CFZ	None	Yes
3	439	507	CFZ, LFX	Bedaquiline discontinued	No
4	411	475	CFZ, LFX	None	Yes
11	442	536	MFX	None because QTc was 432 the day after the peak value	Yes
12	400	610	LFX	K+ = 2.2; bedaquiline stopped and restarted two weeks after K+ replenished	Yes
14	483 (3 months after bedaquiline started)	546 (1 day after bedaquiline was stopped)	MFX, CFZ, Effexor, Zofran	MFX and CFZ stopped sequentially until QTc decreased	Yes

Abbreviations: CFZ, clofazimine; LFX, levofloxacin; K+, potassium; MFX, moxifloxacin; QTc, corrected QT interval.