Safety of prolonged treatment with bedaquiline in programmatic conditions

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Shareable abstract (@ERSpublications)
This study demonstrated that prolonged use of bedaquiline under programmatic conditions appears to be safe. However, clinicians should carefully monitor QTcF interval throughout treatment with bedaquiline due to proven risk of QTcF prolongation. https://bit.ly/36UHHc3

Abstract

Bedaquiline is now considered a first-line medicine for treatment of rifampicin-resistant tuberculosis (RR-TB). We evaluated the safety of treatment with bedaquiline for longer than 190 days in individuals with RR-TB under programmatic conditions.

In a prospective cohort study enrolling pulmonary RR-TB patients, we initiated bedaquiline-based treatment at a tertiary hospital in Belarus. We defined standard bedaquiline use as <190 days and prolonged as ⩾190 days. We recorded adverse events (AEs) and classified their seriousness and relation to bedaquiline. Our primary outcome in regression analyses was the incidence of serious AEs occurring within 5 months of bedaquiline cessation. We used generalised estimating equations to estimate the adjusted incidence rate ratio (aIRR) of serious AEs between the prolonged and standard bedaquiline groups.

We enrolled 113 patients, 83 (73%) of whom received standard and 30 (27%) received prolonged treatment. A total of 2030 AEs occurred during treatment. Of these, 63 (3.1%) were serious AEs occurring within 5 months of bedaquiline cessation; QTcF prolongation was the most common bedaquiline-related serious AE. The incidence of serious AEs per 100 person-months was 5.4 (3.9 to 7.2) in the standard group and 4.4 (2.6 to 7.0) in the prolonged group. In adjusted analyses, serious AEs were no different (aIRR: 0.82, 95% CI 0.42–1.61) in the prolonged group. One patient in the standard bedaquiline group died of acute cardiopulmonary failure deemed possibly related to bedaquiline.

Prolonged use of bedaquiline under programmatic conditions appears safe. Clinicians should carefully monitor QTcF interval since its prolongation was commonly observed.

Introduction

Tuberculosis (TB) remains a major global health problem that is further complicated by the emergence of antimicrobial resistance. TB strains resistant to key drugs, such as rifampicin-resistant (RR)-TB or multidrug-resistant (MDR)-TB, substantially reduce the probability of treatment success. Strains with added resistances to second-line drugs, such as extensively drug-resistant (XDR)-TB, further limit treatment options and probability of success. The most recent data suggest a global treatment success rate of 59% for RR/MDR-TB [1].

Bedaquiline is a drug with antituberculous bactericidal activity approved by the European Medicines Agency in 2013 for treatment of MDR-TB over a period of 24 weeks. It is now considered a first-line medicine for RR/MDR-TB treatment according to the World Health Organisation (WHO) [2, 3]. In 2020,

the WHO allowed off-label prolonged use of bedaquiline, defined as longer than 24 weeks. This recommendation was based on analysis of data derived from the endTB observational study [4, 5]. Prolonged use of bedaquiline is frequently considered by clinicians owing to limited number of options available for treatment of patients with highly resistant TB. However, evidence of the safety of prolonged bedaquiline use under programmatic conditions is limited [6].

The primary objective of our study was to evaluate the safety of prolonged use of bedaquiline, defined as use for >190 days, under programmatic conditions. The secondary objective was to compare incidence of serious adverse events (AEs) and bedaquiline-related AEs experienced among individuals treated with standard and prolonged treatment with bedaquiline.

Material and methods

Study design and population

This was a prospective cohort study using data from a cohort event monitoring study combined with routine data of the programmatic management of drug-resistant TB, defined as all associated functions related to providing services in the country, based on the TB strategy to achieve the targets set for drug-resistant TB in the Global Plan to End TB [6, 7]. The study protocol was approved by the Ethics Committee at the Republican Scientific Practical Centre on Pulmonology and Phthisiatry (RSPCPP) of Belarus. All new and previously treated patients with bacteriologically confirmed pulmonary RR-TB initiating treatment with bedaquiline at RSPCPP, a tertiary care hospital, between March 2015 and June 2016 were consecutively included in the study. Successfully treated patients were followed-up for 24 months for possible recurrence of TB. Patients receiving delamanid concurrently with bedaquiline were excluded from this study.

Definitions

WHO definitions for drug resistance, patient registration groups and treatment outcomes from 2013 were used [8]. Patients with RR-TB, whose isolates were resistant to either a fluoroquinolone or to any of the second-line injectables, but not to both, were defined as having pre-XDR-TB. An adverse event was defined as any untoward medical occurrence that may present in a patient during treatment with TB drugs, but which does not necessarily have a causal relationship with this treatment [9]. A serious event was one which either led to death or a life-threatening experience, hospitalisation or prolongation of hospitalisation, persistent significant disability or a congenital anomaly/birth defect [10]. Severity of the event was classified as mild (grade 1), moderate (grade 2) and severe (grades 3 and 4) according to the Common Terminology Criteria for Adverse Events, version 5 [10, 11].

Study procedures

All bacteriological tests were performed at the Reference Laboratory of the National TB Centre in Minsk, Belarus, which was quality-assured by the Supranational Reference Laboratory in Milan, Italy [12]. Details of bacteriological tests are described in supplementary Appendix 1.

Treatment regimens were individually tailored according to the drug susceptibility profile and contained bedaquiline, linezolid and clofazimine, unless contraindicated. If confirmed susceptible, the regimens had one second-line injectable and/or a fluoroquinolone added to the regimen. Terizidone, pyrazinamide, imipenem-cilastatin with amoxicillin-clavulanate and/or ethionamide/protionamide were added to bring the total number of effective drugs (*i.e.*, defined as drugs to which patient's isolates were not resistant to) in the treatment regimen to six.

The recommended standard duration of bedaquiline use is 24 weeks (168 days) [5]. However, this duration may vary owing to events, such as missed or cancelled clinic visits. Based on a histogram of the duration of bedaquiline use, we grouped the patients according to those who received bedaquiline for <190 days as receiving standard treatment with bedaquiline and those who received bedaquiline for ⩾190 days as receiving prolonged treatment with bedaquiline (histogram presented in supplementary Appendix 2).

The decision to prolong treatment with bedaquiline was based on the following criteria: remaining sputum culture-positive after ⩾3 months of treatment, but not meeting the criteria for treatment failure; fewer than four effective drugs remaining in the treatment regimen if bedaquiline was discontinued; and/or individual risk factors for poor outcomes, such as body mass index (BMI) <18.5 kg/m^2, high pre-treatment sputum smear bacillary load defined semi-quantitatively as 2+ or 3+, HIV-positivity and extensive/advanced pulmonary disease [13]. Injectables were continued throughout the treatment, if tolerated. The overall treatment duration was at least 12 months after the culture conversion for a minimum total treatment duration of 18 months.

Treatment efficacy and safety monitoring was implemented through bacteriological, clinical and laboratory assessment. All assessments were performed at the start of treatment and monitored at least monthly during the treatment and semi-annually post treatment for 24 months (supplementary table S1). AEs were recorded and considered potentially bedaquiline treatment-related if they occurred either during treatment or up to 5 months after bedaquiline was stopped, in view of the prolonged terminal elimination half-life of bedaquiline [14].

The Belarussian national electronic TB registry and national pharmacovigilance electronic database were used for data collection. Pharmacovigilance specialists checked the contents of the data for completeness and accuracy and judged on the severity of all reported AE, as well as performed causality assessment for serious AE.

Data analysis

We compared individuals who received standard treatment with bedaquiline with those who received prolonged treatment. We described each group based on demographic, clinical and treatment-related factors and calculated the number and incidence of all AEs, serious AEs and bedaquiline-related events for each group. We compared groups using two-sided tests: Kruskal–Wallis test for medians, Pearson's chi square test for proportions and Fisher exact test for rates. Uncertainty in incidence rates was calculated using exact Poisson confidence intervals. We calculated the proportion of patients experiencing QTcF >500 ms or an increase by >60 ms from baseline during treatment with bedaquiline.

We then conducted regression analyses to compare patients who completed standard treatment with those who received prolonged treatment. We did this to minimise possible survivor bias from patients who died early in treatment or those who stopped bedaquiline due to a bedaquiline-related AE and therefore never had the opportunity to receive prolonged treatment. We used generalised estimating equations with a Poisson distribution and log-link to estimate incidence rate ratios and their 95% confidence intervals (using robust standard errors). The analyses accounted for clustering at the individual level and used an autoregressive correlation structure. The primary outcome was the incidence of serious AEs occurring within 5 months of bedaquiline cessation, and the secondary outcome was the incidence of serious AEs occurring during receipt of bedaquiline up to day 189.

To construct multivariate models, we first performed univariate analysis on various predictors of our outcomes. The predictors were selected *a priori*, based on the literature, as well as on what we perceived would be known by the treating clinicians [15]. The predictors included: sex (male or female), age (per 10-year increase), use of second-line injectable drugs (yes or no), number of concomitant TB medications (per additional drug), smear-positivity at treatment initiation (yes or no), cavitation on chest radiograph at treatment start (yes or no), BMI (<18.5 or $\geqslant$18.5 kg·m^{-2}), QT interval corrected by the Fridericia's correction formula (QTcF) (per 10-ms increase), alcohol abuse disorder (defined as alcohol use leading to problems in relationships, health, employment or finances within the past year; yes or no), diabetes mellitus (yes or no) and HIV co-infection (yes or no). Multivariate models were constructed including group allocation (*i.e.*, standard *versus* prolonged), age, sex and all predictors with p<0.2 in univariate analysis. We also conducted a sensitivity analysis that included all predictors in multivariate models to see if conclusions might differ.

We conducted a secondary analysis in the prolonged bedaquiline group. We compared the incidence of serious AEs in the first 189 days of treatment *versus* the incidence of serious AEs from day 190 up to 5 months after stopping bedaquiline.

We did a *post hoc* analysis to compare the time to first instance of QTcF prolongation by >60 ms between the standard and prolonged treatment groups among those who had both baseline and at least one QTcF measurement during the treatment. We considered the last QTcF measure as a censoring event. We used Cox proportional hazards model adjusted for the variables considered in our previous multivariate model to estimate the hazard ratio and 95% confidence interval for the incidence of QTcF prolongation by >60 ms between the groups.

All analyses were conducted with R software (version 4.0.0; The R Foundation, Vienna, Austria) using package geepack (version 1.3-1).

Results

Sociodemographic data and disease characteristics

A total of 120 RR-TB patients were treated at the RSPCPP during March 2015 through June 2016. Out of them, seven were excluded from the cohort: five because no bedaquiline was used and two because of

TABLE 1 Characteristics of patients on standard or prolonged treatment with bedaquiline

	Standard treatment with bedaquiline	Prolonged treatment with bedaquiline	Overall	p-value[#]
Patients n	83	30	113	–
Patient characteristics				
Median (IQR) age	37 (29–47)	38 (31–51)	38 (30–47)	0.74
Male	60 (72.3)	21 (70)	81 (71.7)	0.99
HIV infection	4 (4.8)	0 (0)	4 (3.5)	0.52
Thyroid disease	3 (3.6)	0 (0)	3 (2.7)	0.69
Alcohol abuse disorder	11 (13.3)	6 (20)	17 (15)	0.56
Diabetes	6 (7.2)	1 (3.3)	7 (6.2)	0.75
Median (IQR) baseline QTcF interval[¶]	388 (360–407)	386 (362–416)	387 (360–410)	0.63
Microbiological/radiological findings				
AFB smear-positive at baseline[+]	21 (25.3)	23 (76.7)	44 (38.9)	<0.01
Cavitation on chest radiograph	50 (60.2)	22 (73.3)	72 (63.7)	0.29
Previous treatment				
Never previously treated for TB	9 (10.8)	1 (3.3)	10 (8.8)	0.39
Previously treated with first-line drugs	12 (14.5)	1 (3.3)	13 (11.5)	0.19
Previously treated with second-line drugs	62 (74.7)	28 (93.3)	90 (79.6)	0.06
DST				
DST performed for fluoroquinolones	78 (94)	30 (100)	108 (95.6)	0.39
If DST performed, fluoroquinolone resistant	67 (85.9)	27 (90)	94 (87)	0.80
DST performed for second-line injectables	79 (95.2)	30 (100)	109 (96.5)	0.52
If DST performed, second-line injectable resistant	60 (75.9)	22 (73.3)	82 (75.2)	0.97

Data reported as n (%) unless otherwise specified. HIV: human immunodeficiency virus; AFB: acid-fast bacilli; TB: tuberculosis; DST: drug susceptibility test. [#]: the following tests were used to calculate p-value: for medians Kruskal–Wallis Test; for proportions Chi square test; for rates Exact Fisher two-sided test. [¶]: missing for five patients (two in the bedaquiline 6 months group and three in the bedaquiline >6 months group). [+]: missing for one patient (one in the bedaquiline 6 months group).

getting delamanid in addition to bedaquiline. A total of 113 patients with pulmonary RR-TB were subjected to the analyses. Of these, 83 (73.5%) received standard treatment with bedaquiline and 30 (26.5%) received prolonged treatment. The proportion of patients who were smear-positive (p<0.01) at the start of treatment was higher among the patients who received prolonged treatment (table 1). Other characteristics did not significantly differ between the treatment groups.

Treatment

Characteristics of the treatment regimen and outcomes are reported in table 2. The number of effective drugs included in the initial regimen was six in both groups. The median total treatment duration was 24.2 months among those who received prolonged treatment with bedaquiline and 23.7 months among those who received standard treatment (p<0.01). The median (IQR) duration of bedaquiline use among those receiving prolonged bedaquiline was 8.0 (7.3–9.2) months. The duration of receiving second-line injectables was also significantly longer among those receiving prolonged bedaquiline (median 13.8 months *versus* 5.3 months; p=0.02). Treatment success was equivalent between groups (92.8% among standard duration *versus* 96.7% among prolonged duration; p=0.92). There was no recurrent TB among successfully treated patients during the follow-up period of 24 months.

Safety profile
Any adverse event

The most common AEs observed among patients were elevated liver enzymes, eosinophilia, ECG abnormalities including prolongation of the QTcF, electrolyte disorders, hyperuricaemia, hyperglycaemia, and elevated creatinine and alkaline phosphatase. Details of the AEs recorded during the treatment are presented in table 3, while the complete list of events and their classification as per system organ class and category is presented in supplementary Appendix 3.

TABLE 2 Regimen received and treatment outcomes among patients on standard and prolonged treatment with bedaquiline

	Bedaquiline <190 days		Bedaquiline >190 days		p-value[#]
Patients n	83		30		
Regimen duration					
Median (IQR) total treatment duration, months	23.7 (20.7–24.0)		24.2 (23.8–24.9)		<0.01
Median (IQR) treatment duration with bedaquiline, months	5.5 (5.4–5.6)		8.0 (7.3–9.2)		<0.01
Median (IQR) treatment duration with linezolid, months[¶]	23.5 (20.1–24.0)		24.1 (23.7–24.4)		<0.01
Median (IQR) treatment duration with injectables, months[+]	5.3 (5.3–21.2)		13.8 (10.7–24.2)		0.02
Treatment outcomes					
Number with treatment success	77 (92.8)		29 (96.7)		0.75
Number with failure	1 (1.2)		0 (0)		1
Number dying during treatment	3 (3.6)		1 (3.3)		1
Number lost to follow-up	2 (2.4)		0 (0)		0.96
Regimen received	**Initial**	**Added during treatment**	**Initial**	**Added during treatment**	
Number of drugs in initial regimen, median (IQR)	6 (5–6)	–	6 (6–6)	–	0.80
Included moxifloxacin or levofloxacin or gatifloxacin	11 (13.3)	43 (51.8)	0 (0)	15 (50)	0.08
Included linezolid	83 (100)	0 (0)	29 (96.7)	1 (3.3)	0.59
Included clofazimine	80 (96.4)	1 (1.2)	27 (90)	2 (6.7)	0.39
Included terizidone	82 (98.8)	0 (0)	28 (93.3)	2 (6.7)	0.35
Included amikacin or capreomycin or kanamycin	32 (38.6)	6 (7.2)	14 (46.7)	10 (33.3)	0.58
Included pyrazinamide	54 (65.1)	2 (2.4)	23 (76.7)	0 (0)	0.35
Included imipenem/cilastatin with amoxicillin and clavulanic acid	42 (50.6)	2 (2.4)	16 (53.3)	7 (23.3)	0.97
Included ethionamide or prothionamide	8 (9.6)	8 (9.6)	2 (6.7)	3 (10)	0.91

Data reported as n (%) unless otherwise specified. [#]: the following tests were used to calculate p-value: for medians Kruskal–Wallis test; for proportions Chi square test; for rates exact Fisher two-sided test. For the regimen received, p-value only refers to initial regimen. [¶]: all patients received linezolid during treatment. [+]: only if received injectables ever during treatment (n=35 bedaquiline 6 months; n=20 bedaquiline >6 months; n=55 overall).
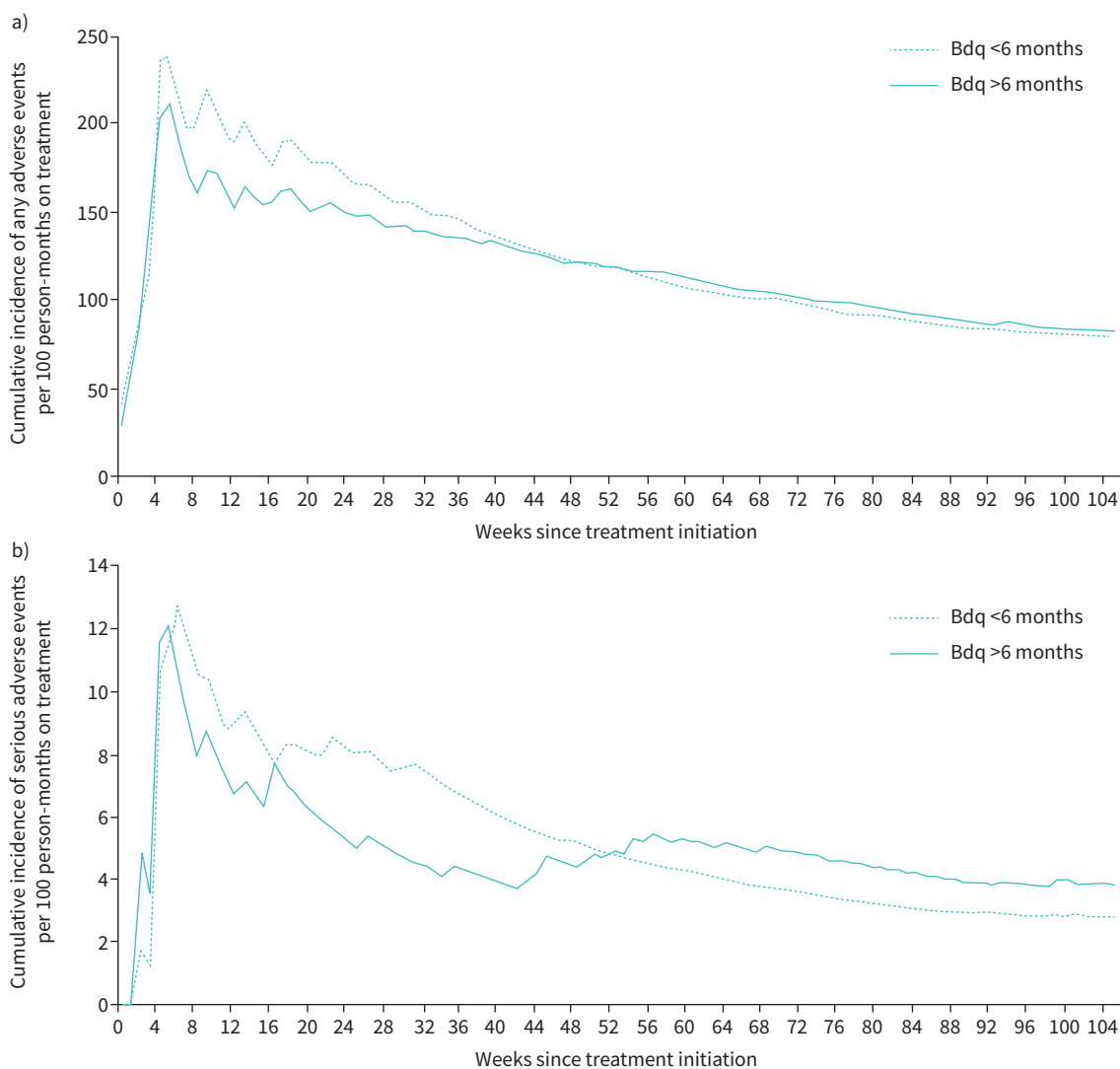
TABLE 3 All adverse events registered during the treatment course among patients on standard and prolonged treatment with bedaquiline

	Bedaquiline <190 days	Bedaquiline ≥190 days	Overall	p-value[#] between standard and prolonged
Number of patients	83	30	113	–
Total treatment duration months	1807.8	722.7	2530.5	–
Total treatment with bedaquiline months	440.3	257.2	697.5	–
All adverse events				
Patients experiencing any adverse event	81 (97.6)	28 (93.3)	109 (96.4)	–
Events during treatment total	1448	585	2033	–
Incidence per 100 person-months (95% CI)	80.1 (76.0–84.3)	80.9 (74.5–87.8)	80.3 (76.9–83.9)	0.83
Adverse events during periods of treatment				
Events with bedaquiline up to day 190 of treatment	783	280	1063	–
Incidence per 100 person-months (95% CI)	177.8 (165.6–190.7)	150.1 (133.1–168.8)	169.6 (159.5–180.1)	0.01
Events with bedaquiline from day 190 to cessation	N/A	62	62	–
Incidence per 100 person-months (95% CI)	N/A	87.8 (67.3–112.6)	87.8 (67.3–112.6)	–
Events after stopping bedaquiline up to 5 months after bedaquiline cessation	288	120	408	–
Incidence per 100 person-months (95% CI)	81.5 (67.5–97.4)	72.7 (64.5–81.6)	75.1 (68.0–81.6)	0.31
Events >5 months after stopping bedaquiline, to end of treatment	377	123	500	–
Incidence per 100 person-months (95% CI)	38.8 (35.0–42.9)	38.7 (32.1–46.1)	38.8 (35.4–42.3)	0.97
All events during bedaquiline	783	342	1125	–
Incidence per 100 person-months (95% CI)	177.8 (165.6–190.7)	133.0 (119.2–147.8)	161.3 (152.0–171.0)	<0.001
All events up to 5 months after stopping bedaquiline	1071	462	1533	–
Incidence per 100 person-months (95% CI)	128.0 (1120.5–135.9)	114.2 (104.0–125.1)	123.5 (117.4–129.9)	0.04
Bedaquiline-related adverse events				
Patients with at least one bedaquiline-related adverse event	12	3	15	–
Number of bedaquiline-related adverse events up to 5 months after bedaquiline cessation	25	4	29	–
Incidence per 100 person-months (95% CI)	3.0 (1.9–4.4)	1.0 (0.3–2.5)	2.3 (1.6–3.4)	0.01
Category of adverse events				–
QTcF prolongation	18 (72)	4 (100)	22 (75.7)	–
Liver enzyme elevation	3 (12)	0 (0)	3 (10.3)	–
Hyperuricaemia	1 (4)	0 (0)	1 (3.4)	–
Pancreatitis	1 (4)	0 (0)	1 (3.4)	–
Anxiety	1 (4)	0 (0)	1 (3.4)	–
Cardiac failure	1 (4)	0 (0)	1 (3.4)	
Patients stopping treatment due to bedaquiline-related adverse event	6	0	6	–
Median (IQR) months to bedaquiline cessation	5.5 (5.1–5.5)	N/A	5.5 (5.1–5.5)	–

Data reported as n (%) unless otherwise specified. [#]: exact Fisher two-sided test was used to calculate p-value.

More than 90% of patients in both groups experienced at least one AE during treatment with a total of 2030 events registered. There was no statistically significant difference in total incidence of any AE during treatment among patients who received the prolonged treatment with bedaquiline compared to those who received standard treatment (80.9 versus 80.1 per 100 person-months of treatment; p=0.83). However, when comparing those AEs that occurred within 5 months of cessation of bedaquiline, significantly more events occurred in the standard bedaquiline group than in the prolonged group (128.0 versus 114.2 per 100 person-months of treatment, respectively; p=0.04). The cumulative incidence of any AE appeared similar between the groups during treatment (figure 1a).

The incidence of any bedaquiline-related AE within 5 months of stopping bedaquiline was significantly higher among patients who received standard treatment versus those who received prolonged treatment with bedaquiline (3.0 versus 1.0 per 100 person-months, respectively; p=0.01). QTcF prolongation was the most common bedaquiline-related AE in both groups. This accounted for 72% of events in the standard

FIGURE 1 Cumulative rates of a) any and b) serious adverse events during treatment, stratified by the duration of bedaquiline (Bdq) exposure.

Patients on treatment																										
Bdq <6 months	83	83	82	82	82	80	80	80	80	79	79	79	79	79	78	78	78	77	77	77	75	71	66	61	56	51	40
Bdq >6 months	30	30	30	30	30	30	30	30	30	30	30	30	30	29	29	29	29	28	28	28	28	28	28	28	27	27	23
Patients on bedaquiline																										
Bdq <6 months	83	83	81	79	79	79	73	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bdq >6 months	30	30	30	30	30	30	30	30	26	14	11	3	2	2	2	1	1	1	1	1	0	0	0	0	0	0	0

treatment group (median time to event 102 days (IQR 35–142 days)) and 100% of the events in the prolonged treatment group (median time to event 112 days (IQR 109–135 days)). A total of six persons stopped bedaquiline due to a bedaquiline-related AE in the standard group, while no patients stopped bedaquiline due to a bedaquiline-related event in the prolonged group.

Serious adverse events

Serious AEs are described in table 4; the complete list of registered serious events occurring up to 5 months after bedaquiline cessation (n=63) are provided in supplementary table S2. We did not observe a significant difference in the incidence of serious AEs between the standard and prolonged bedaquiline groups during treatment (2.8 *versus* 3.6 per 100 person-months; p=0.30). This was consistently found when limiting analysis to the first 190 days of treatment (7.5 *versus* 5.4 per 100 person-months of treatment; p=0.07). There was no significant difference between the groups in serious AEs for up to 5 months after bedaquiline cessation (5.4 *versus* 4.4 per 100 person-months; p=0.48).

Among patients who experienced a serious AE within 5 months of stopping bedaquiline, the median time to the first serious AE was 91 days in the standard treatment group and 112 days in the prolonged treatment group. The most common serious AEs among these persons in the standard treatment group were liver enzyme elevation (35.5%), eosinophilia (17.8%) and hypokalaemia (13.3%). In the prolonged treatment group, they were QTcF prolongation (27.8%) and hypokalaemia (22.2%). The cumulative incidence of serious AEs was lower in the prolonged group early in treatment but surpassed the standard group in ~1 year.

The incidence of serious bedaquiline-related AEs did not differ between the standard and prolonged treatment groups (0.7 *versus* 0.2 per 100 person-months; p=0.22). The QTcF prolongation was the most common serious bedaquiline-related AE in both groups. One patient stopped bedaquiline due to a serious bedaquiline-related AE in the standard duration group.

QTcF changes throughout the treatment

Among the 108 patients with the baseline QTcF interval measurements available, the mean±SD estimate was 385.7±33.9 ms (table 5). After 1 month of treatment with bedaquiline, the QTcF intervals had increased by an average of 17.6±24.4 ms and appeared to continually increase throughout the treatment to reach a maximum of 61.9±49.1 ms in the 9th month of treatment. While the QTcF prolongations of 60 ms above the baseline were common, only one patient developed a prolongation of the QTcF interval up to >500 ms during the treatment. Monthly QTcF intervals were largely similar between standard and prolonged treatment groups (supplementary Appendix 3). When the prolonged and standard treatments were compared using Cox proportional hazard models, there was no significant difference for the rate of QTcF prolongation by >60 ms above the baseline between the standard group (10 events per 100 person-months) and the prolonged group (14.8 events per 100 person-months), with an adjusted hazard ratio of 1.16 (95% CI 0.56–2.42).

Deaths

Four deaths occurred among the 113 patients, one in the prolonged group and three in the standard group. The death in the prolonged group occurred in a 31-year-old woman due to sudden death from a pulmonary thromboembolism and cardiac failure 350 days after initiating treatment. The patient had received 223 days of bedaquiline treatment; hence, the event was deemed unlikely to be related to bedaquiline.

Two deaths in the standard group were deemed unlikely to be related to bedaquiline. A 50-year-old woman received bedaquiline for 47 days, and on day 112 of treatment she died due to a pre-existing neoplasm. A 42-year-old man received bedaquiline for 175 days but died on day 799 of treatment as a result of respiratory failure owing to progression of tuberculosis.

One death in the standard group was deemed possibly related to bedaquiline. A 41-year-old man receiving a regimen of bedaquiline, pyrazinamide, linezolid, clofazimine, terizidone, imipenem-cilastatin and amoxicillin-clavulanate died 42 days after initiating treatment due to acute cardiopulmonary failure. The patient had ankylosing spondylitis and a history of alcohol abuse. The patient's QTcF measurement taken on the day of treatment initiation was 428 ms; the last QTcF measurement was performed 15 days before his death and the result was 441 ms.

Regression analyses

The regression analyses included 30 patients in the prolonged treatment group and 75 patients in the standard treatment group (table 6). Multivariate regression analyses showed that the persons who received

TABLE 4 Serious adverse events registered during the treatment course among patients on standard and prolonged treatment with bedaquiline				
	Bedaquiline <190 days	Bedaquiline ≥190 days	Overall	p-value[#] between standard and prolonged
Number of patients	83	30	113	–
Total treatment duration months	1807.8	722.7	2530.5	–
Total treatment with bedaquiline months	440.3	257.2	697.5	–
Total treatment up to 5 months after bedaquiline cessation, months	836.5	404.4	1240.9	–
Serious adverse events				
Patients experiencing any serious adverse event	32 (38.6)	16 (53.3)	48 (42.5)	–
Events during treatment total	50	26	76	–
Incidence per 100 person-months (95% CI)	2.8 (2.1–3.6)	3.6 (2.4–5.3)	3.0 (2.4–3.8)	0.30
Serious adverse events during periods of treatment				
Events with bedaquiline up to day 190 of treatment	37	10	47	–
Incidence per 100 person-months (95% CI)	7.5 (5.5–10.0)	5.4 (2.6–9.9)	8.4 (5.9–11.6)	0.07
Events with bedaquiline from day 190 to cessation	N/A	0	0	–
Incidence per 100 person-months (95% CI)	N/A	0 (0–5.2)	0 (0–5.2)	–
Events after stopping bedaquiline up to 5 months after bedaquiline cessation	8	8	16	–
Incidence per 100 person-months (95% CI)	2.0 (0.9–4.0)	5.4 (2.3–10.7)	2.9 (1.7–4.8)	0.10
Events > 5 months after stopping bedaquiline, to end of treatment	5	8	13	–
Incidence per 100 person-months (95% CI)	0.5 (0.2–1.2)	2.5 (1.1–5.0)	1.0 (0.5–1.7)	0.03
All events up to 5 months after stopping bedaquiline	45	18	63	–
Incidence per 100 person-months (95% CI)	5.4 (3.9–7.2)	4.4 (2.6–7.0)	5.1 (3.9–6.5)	0.48
Bedaquiline-related serious adverse events				
Patients with at least one bedaquiline-related serious adverse event	5	1	6	–
Number of bedaquiline-related serious adverse events up to 5 months after bedaquiline cessation	6[¶]	1	7	–
Incidence per 100 person-months (95% CI)	0.7 (0.3–1.6)	0.2 (0.1–1.4)	0.6 (0.2–1.2)	0.22
Category of serious adverse events				–
QTcF prolongation	2 (33.3)	1 (100)	3 (42.8)	–
Liver enzyme elevation	1 (16.7)	0 (0)	1 (14.3)	–
Pancreatitis	1 (16.7)	0 (0)	1 (14.3)	–
Hyperuricaemia	1 (16.7)	0 (0)	1 (14.3)	–
Cardiac failure	1 (16.7)	0 (0)	1 (14.3)	–
Patients stopping treatment due to bedaquiline-related serious adverse event	1	0	1	–
Months to bedaquiline cessation	1.4	N/A	N/A	–

Data reported as n (%) unless otherwise specified. [#]: exact Fisher two-sided test was used to calculate p-value; [¶]: patient experienced two serious adverse events: the first was hyperuricaemia 21 days into treatment and the second was aspartate aminotransferase elevation 147 days into treatment.

TABLE 5 Change in mean QTcF interval by month of treatment[#]

Month	Number of patients with measure	Mean±SD maximum QTcF measure	Mean±SD change in QTcF from baseline	Mean±SD change in QTcF from previous month	Number of patients (%) with QTcF that is >60 ms from baseline
Baseline	108	385.7±33.9	–	–	–
1	105	402.5±33.1	17.6±24.4	17.6±24.4	6 (5.7)
2	77	414.6±28.7	26.5±33.9	10.1±32.4	12 (15.6)
3	94	416.1±32.1	28.5±36.9	3.2±30.1	21 (22.3)
4	86	420.8±33.4	34.2±37.4	8.2±33.4	22 (25.6)
5	89	422.7±29	33.8±38.5	1.0±33.6	21 (23.6)
6	61	426±29.6	40.2±40.7	4.2±27.0	14 (23)
7	24	418.5±34.6	34.1±57.4	−15±36.8	8 (33.3)
8	12	411.2±32.6	24.8±42.5	1±24.0	3 (25)
9	10	434.1±28.4	61.9±49.1	11.7±31.9	5 (50)
10	4	442±15.6	58.8±35.4	9.5±9.0	1 (25)

ECG measures done on the same day were averaged to arrive at an estimate. [#]: only one patient included in months 11 and beyond.

prolonged treatment with bedaquiline *versus* those who received standard treatment did not experience a significantly different incidence in serious AEs either within the first 190 days of exposure to bedaquiline (incidence rate ratio (IRR) 0.73, 95% CI 0.33–1.61) or up to 5 months after the cessation of bedaquiline (IRR 0.82, 95% CI 0.42–1.61). Other factors associated with AEs for both primary and secondary outcomes are reported in supplementary tables S3 and S4. In our secondary analysis, we did not observe any significant difference in the incidence of serious AEs between the first 190 days of treatment and treatment after this time-point (IRR 0.75, 95% CI 0.30–1.88) among persons receiving prolonged bedaquiline treatment (supplementary table S5).

Discussion

Our prospective study shows that the prolonged use of bedaquiline appears to be safe under programmatic conditions with rigorous oversight and pharmacovigilance. Multivariate statistical methods allowed us to control for concomitant anti-TB medication and to compare events associated with standard and/or prolonged use of bedaquiline. There was no significant difference identified in incidence of overall and bedaquiline-related serious events during treatment among the patients who received prolonged treatment with bedaquiline compared to those who received standard treatment. These findings concur with similar conclusions from retrospective studies using spontaneously reported cases [13, 16]. Considering the fact that the terminal half-life of bedaquiline has been estimated to be 5.5 months, we also identified that the incidence of serious events was not different when analysed within 5 months of bedaquiline cessation [17].

Bedaquiline was deemed to be related to <10% of all serious AEs registered in our study. However, bedaquiline was responsible for approximately half of all serious QTcF interval prolongations, and one

TABLE 6 Primary and secondary multivariate analyses

Outcome	Events/person-months	Events/person-months	Multivariate IRR (95% CI)
Serious adverse events	Standard treatment with bedaquiline[#]	Prolonged treatment with bedaquiline	
Up to 5 months after bedaquiline cessation	38/767	18/405	0.82 (0.42–1.61)
Within the first 190 days of treatment	33/410	10/187	0.73 (0.33–1.61)
Serious adverse events	Within the first 190 days of treatment	From day 190 until 5 months after bedaquiline cessation	
Among persons receiving prolonged treatment	10/187	8/212	0.75 (0.30–1.88)

[#]: reference group.

death occurred in the standard group due to sudden death. In both groups, QTcF prolongation was the most common bedaquiline-related AE overall and bedaquiline-related serious event in particular. While increases in QTcF interval up to 20 ms have been commonly described, a continual increase throughout the treatment that surpassed 60 ms above the baseline by the 9th month of treatment has not been reported previously [24]. Although in the present study the risk of QTcF prolongation was not significantly higher in those patients who received bedaquiline for a prolonged period, the finding of a continual increase in QTcF may still be of concern in view of the number of patients who receive standard RR-TB regimens of a duration of 9 to 12 months with inclusion of bedaquiline throughout the whole course of the treatment [4]. Cardiotoxic effects of the currently recommended RR-TB treatments are potentially impacted by the concomitant use of fluoroquinolones and clofazimine [13, 18–24]. Moreover, there is a long list of auxiliary medicines that are associated with the QTcF interval prolongation [25]. The higher number of QTcF-prolonging anti-TB medicines used in the standard bedaquiline treatment group causing additive cardiotoxic action can explain the more frequent non-serious QTcF prolongation observed in this group of patients. Our current finding further emphasises the need for performing an ECG on a regular basis for strict monitoring of QTcF interval. This also supports the requirement for ECG monitoring in programmes that use bedaquiline for a prolonged period to ensure accessibility of cardioversion to manage torsades de pointes and cardiac arrest [3]. Hence, management of patients with prolonged QTcF interval requiring life-saving anti-TB treatment needs a multidisciplinary approach including meticulous revision of medicines used for concomitant diseases, as well as consultations with a cardiologist about the need for a temporary or permanent pacemaker to prevent deadly arrhythmias. According to available literature, alcohol abuse observed in our study population may also contribute to cardiotoxicity, necessitating joint intervention with services for addictive behaviours [26–30]. According to CTCAE 5.0, which is the currently recommended scale for grading AEs and is used for reporting within this study, QTc interval prolongation >60 ms compared to baseline is defined as grade 3 AE. At the same time, earlier studies reporting QTc interval prolongation use the older version of grading scale CTCAE 4.0, where prolongation >60 ms compared to baseline without Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia was not considered to be an AE [13, 15]. This potentially caused underreporting of severe QTc prolongation.

The finding that the majority of patients in both groups of our study experienced at least one AE coincides with well-documented toxicity of long-term anti-TB treatment [15, 31, 32]. The most common serious AEs not necessarily related to bedaquiline were liver enzyme elevation, eosinophilia and hypokalaemia. In contrast to what was observed within the period of bedaquiline treatment, the number of total non-serious AEs within 5 months after cessation of bedaquiline was significantly higher in the standard bedaquiline group. This can be explained by earlier replacement of bedaquiline and longer use of other anti-TB medicines with worse safety profiles, such as thiamide, second-line injectables, P-aminosalicyclic acid (PAS), pyrazinamide or carbapenems, in the regimen [15, 18, 32–35].

We found that second-line injectables were strongly associated with serious AEs throughout treatment. Extreme toxicity of injectables has already triggered initiatives on fully oral RR-TB treatment, but there is still a lack of anti-TB medicines that could be used instead in highly resistant cases, urging further developments in the field [5, 36–38].

This was not a randomised study, and the results may have been biased by the fact that the decision to continue with prolonged use of bedaquiline might have been affected by better tolerability of bedaquiline by the respective patients and better survival during the first 190 days of treatment, as compared to those patients who did not continue with bedaquiline. However, efforts were made to mitigate this bias with the statistical analysis, as were groups similar for the majority of other parameters.

Conclusion

In conclusion, this study demonstrated that prolonged use of bedaquiline under programmatic conditions with pharmacovigilance appears to be safe. Clinicians should carefully monitor QTcF interval throughout treatment with bedaquiline because of the risk of QTcF prolongation. Further studies are needed to establish strategies to manage prolonged QTcF interval during prolonged treatment with bedaquiline.

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