Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis

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SUMMARY OF THE ARTICLE:

Treatment regimens including prolonged bedaquiline use are effective and overall well-tolerated in MDR-TB patients.

ABSTRACT:

Bedaquiline, a recently-approved drug for the treatment of multidrug-resistant tuberculosis (MDR-TB), is recommended for a duration of 24 weeks. There is scarce data on patients treated with this drug outside clinical trials.

All MDR-TB patients who started treatment from 01/01/2011 to 31/12/2013 and received ≥30 days of bedaquiline were included in a multicentre observational cohort.

Among 45 MDR-TB patients, 53% harbored isolates resistant to both fluoroquinolones and second-line injectables and 38% to one of these drug classes. Median bedaquiline treatment duration was 361 days, and 33 patients (73%) received prolonged (>190 days) bedaquiline treatment. Overall, 36 patients (80%) had favorable outcome, five were lost-to-follow-up, three died, and one failed and acquired bedaquiline resistance. No cases of recurrence were reported. Severe and serious adverse events were recorded in 60% and 18% of patients. QTcF>500ms values were recorded in 11% of patients, but neither arrhythmias nor symptomatic cardiac side effects occurred. Bedaquiline was discontinued in three patients following QTcF prolongation. No significant differences in outcomes, or adverse events rates were observed between patients receiving standard and prolonged bedaquiline treatment.

Bedaquiline-containing regimens achieved favourable outcomes in a large proportion of patients. Prolonged bedaquiline treatment was overall well-tolerated in this cohort.

INTRODUCTION:

According to the World Health Organisation (WHO), in 2014 480000 people were newly diagnosed with multidrug-resistant tuberculosis (MDR-TB), defined by resistance to isoniazid and rifampicin. Among MDR-TB cases, 9% had extensively drug-resistant tuberculosis (XDR-TB) (resistance to any fluoroquinolone and any second-line injectable drug).[1] MDR-TB treatment outcomes, although heterogeneous in different settings, are overall unsatisfactory. A meta-analysis of MDR-TB patients showed that treatment success rate was 64% with individualised regimens and 54% with standardized treatment.[2] Two large meta-analyses comprising individual patient data consistently found an overall treatment success rate of 54% and 56%.[3,4] Treatment outcomes of XDR-TB are abysmal, ranging from 27% to 40%.[3,5] A study assessing the long-term outcomes of XDR-TB patients reported 11% of favourable outcomes and 73% mortality at 5 years of follow-up.[6]

In order to face this emerging challenge, old drugs have been re-purposed, and new drugs have been developed. Bedaquiline and delamanid have been recently approved for the treatment of MDR-TB. A Phase II trial showed that bedaquiline improves treatment outcomes when compared to placebo.[7] In an uncontrolled Phase II study, bedaquiline plus optimised background regimens achieved favourable outcomes in 62.5% of patients.[8] Preliminary reports of bedaquiline compassionate use programs confirm these promising results.[9-15] However, interim results also underline the risk of experiencing culture reversion after the discontinuation of bedaquiline.[10] To date, WHO recommends the use of bedaquiline for a maximal duration of 24 weeks[16] as no evidence is available supporting a longer use, except for a recent case report.[17] Nausea and hepatitis are the most common side effects associated with bedaquiline.[7-9] However, the main safety concern is cardiotoxicity. Although no serious cardiac events or arrhythmias have been reported to date, bedaquiline has been shown to prolong the QT interval, and the association with other drugs (such as clofazimine or moxifloxacin) can enhance this effect.[8,9] Due to the long terminal half-life of bedaquiline, a cumulative effect of prolonged bedaquiline administration on QT interval could be postulated. We previously reported the interim analysis of a cohort of MDR-TB patients receiving bedaquiline-containing regimens, with six-month culture conversion rates of 96% and no relevant safety signals.[9] The flexibility of the regulatory framework of the compassionate use program in France has allowed the off-label use of bedaquiline beyond 24 weeks in selected patients. The aim of this observational analysis is to complement our previous findings with the evaluation, in a bigger cohort and up to 24 months after treatment completion, of the treatment outcome and safety profile of individualized anti-TB regimens containing prolonged bedaquiline treatment.

METHODS:

Patients and treatment

A retrospective cohort was established including all MDR-TB patients treated with bedaquiline from January, 2011, to December, 2013, and hospitalised at three French referral TB centres (Bligny, Pitié-Salpêtrière and Bichat Hospitals). Patients were followed up after the end of treatment for up to 24 months or to the censor date (March 31, 2016). All TB cases were culture-proven. Standard definition of MDR and XDR were used. Treatment outcomes were assigned according to WHO definitions.[16] At the end of treatment, favourable outcomes were defined as the sum of cured and treatment completed; all other outcomes were defined as unfavourable. All patients with favourable outcomes were re-assessed at 12 and 24 months after end of treatment.

The treatment regimen was designed for each patient according to clinical features, phenotypic and genotypic drug susceptibility testing (DST) results with the advice of the MDR-TB Consilium of the National Reference Centre, which assessed the eligibility for bedaquiline treatment and its prolongation beyond 24 weeks. The criteria that were used to identify eligible patients for bedaquiline prolongation were the following: delayed microbiological response, weak treatment regimens due to intolerance or drug resistance, and/or individual risk factors for poor outcomes (Table 1). In addition, all WHO-recommended requirements for bedaquiline use were met, including active pharmacovigilance and treatment monitoring.[16]

Bedaquiline was provided in the framework of the compassionate use program, and was administered as recommended by the manufacturer. Standard bedaquiline treatment was defined as ≤190 days, representing the standard duration of 24 weeks plus a buffer period of 3 weeks needed by the Consilium to assess bedaquiline treatment duration. Prolonged bedaquiline treatment was defined as >190 days. All drugs were administered as directly-observed treatment during hospitalisation. Treatment and hospitalisation were offered free-of-charge to all patients, including migrants and refugees. All patients were informed regarding the mechanism of the compassionate use program and the safety profile of all drugs in the treatment regimen including bedaquiline. Data were retrospectively extracted from medical records. Human research ethics approval for the study was granted by the Institutional Review Board of the Bligny Hospital.

Procedures

Sputum smear and culture examinations were performed at treatment start, fortnightly up to culture conversion, and monthly thereafter. Time to smear/culture conversion was measured from treatment start to the first of two consecutive negative smear/culture results. Phenotypic DST for a panel of first- and second-line anti-TB drugs was performed at the National Reference Centre using the proportion method on Löwenstein-Jensen medium.[18] Genotypic DST was obtained with commercially-available line probe assays (GenoType® MTBDRplus, GenoType® MTBDRsl, Hain Lifescience, GmbH, Germany) or DNA sequencing. From March 2013 onward, bedaquiline DST was performed on Löwenstein-Jensen medium using the proportion method and a 64 mg/L critical concentration for screening. Resistance was subsequently confirmed in TH11 medium. Bedaquiline DST was performed at baseline and repeated in case of suspicion of treatment failure. A standard 12-lead electrocardiogram was performed at baseline, at two weeks of treatment and monthly thereafter. QT interval correction was calculated according to Fridericia (QTcF) and Bazett (QTcB) formula.[19] A prolongation of the QT interval was defined as ≥60 ms increase during treatment. All adverse events were defined and graded according to severity and seriousness on the basis of the US National Institutes of Health Common Terminology Criteria for Adverse Events, version 4.0.[20] Severe adverse events were defined as any event graded as level three, four, or five. Causality of adverse events was evaluated according to the WHO-UMC system for standardised case causality assessment.[21]

Statistical analysis

Categorical variables were compared by using Fisher's exact test. Continuous variables were reported as median and interquartile range (IQR), and compared by using the two-sample Wilcoxon-Mann-Whitney test. Kaplan-Meier curves for culture conversion were estimated. The Mantel-Cox test was used to compare time to culture conversion. The association between variables and time to culture conversion was studied with a Cox proportional hazards model. Multivariable logistic regression was used to estimate the association of QT interval prolongation and explanatory variables. Variables associated in univariate analysis ($p<0.20$) were considered for backward multivariable analysis. P-values <0.05 were considered as significant. Statistical analysis was performed using STATA (StataCorp, Texas, USA). Results are reported according to the STROBE guidelines for observational cohort studies.

RESULTS:

Socio-demographic and disease characteristics

Among the 102 MDR-TB patients managed in the three centres during the study period, 45 patients (44.1%) were treated with bedaquiline: 36 (80.0%) were born in Eastern Europe/Caucasus countries (Table 2). Coinfection with HCV and HIV was present in 21 (46.7%) and two (4.4%) patients, respectively. 34 (75.6%) patients previously received TB treatment. Overall, 44 patients had pulmonary TB: 39 (88.6%) had lung cavities and 36 (81.8%) bilateral lung involvement. More detailed baseline characteristics are reported in Supplementary Table 1.

Resistance patterns and treatment

A majority of the patients had XDR-TB (n=24, 53.3%). Out of the remaining patients, 11 (24.4%) had strains with additional resistance to fluoroquinolones, and six (13.3%) to any second-line injectable. Four (8.9%) had intolerance to either fluoroquinolones or second-line injectables. The strains showed phenotypical resistance to a median of nine (IQR 7-11) drugs and a median of five (4-6) mutations in resistance-conferring genes. All tested strains were susceptible to bedaquiline at baseline (Table 3). The most frequently prescribed companion drugs are listed in Table 2. Median treatment duration was 624 days (IQR 546-730); injectables were administered for a median of 341 days (IQR 228-455). The median duration of bedaquiline administration was 360 days (range, 31-768). 15 patients (33.3%) received bedaquiline for the full treatment duration. Lung surgery, mostly lobectomy, was performed in 12 (26.7%) patients after a median of 170 days (IQR 75-269) from treatment start, and after sputum culture conversion in 75% of cases.

Treatment safety profile

During treatment, 44 (97.8%) patients experienced at least one adverse event (Table 4). The most frequent were gastrointestinal side effects (n=32, 71.1%), oto-vestibular impairment (n=25, 55.6%)

and peripheral neuropathy (n=18, 40.9%). Severe and serious adverse events were recorded in 27 (60.0%) and seven (17.8%) patients, respectively. The most common severe adverse events were peripheral neuropathy (n=13) and QTc prolongation (n=8). Severe and serious adverse events are detailed in Supplementary Table 2. Bedaquiline was discontinued in three (6.7%) patients due to QTc prolongation after 31, 203, and 279 days of treatment, respectively. One patient experienced uncomplicated pancreatitis few weeks after bedaquiline discontinuation.

With regards to QT interval, only QTcF results will be reported, as no significant difference between QTcF and QTcB results was observed. Figure 1 shows the evolution of QTcF during treatment in the cohort. Overall, QTcF prolongation occurred in 13 (28.9%) patients. QTcF >500ms values were recorded in five (11.1%) patients, all belonging to the prolonged bedaquiline group; in three cases the QTcF prolongation occurred during the first 24 weeks of treatment. Median QTcF values remained stable during the whole treatment duration in the prolonged bedaquiline group. The median of the maximum QTcF increase was 36.2 (IQR 17.9-68.5) ms. In logistic regression analysis, both QTcF >60 ms increase and QTcF >500 ms values were independently associated with co-administration of moxifloxacin at 800 mg/day after adjustment for age, sex and treatment with other QT-prolonging drugs. Methadone treatment was equally associated with >500 ms QTcF values. No association was found with treatment with clofazimine, levofloxacin or moxifloxacin at 400 mg/day. The median of the maximum QTcF increase during treatment was significantly higher in patients treated with high-dose moxifloxacin treatment (data not shown). Neither clinical arrhythmia nor any cardiac event were observed.

Treatment outcomes

Out of 41 patients with positive sputum cultures at treatment start, 23 (56.1%) and 40 (97.6%) achieved culture conversion at 90 and 180 days, respectively. One patient achieved culture conversion at eight months of treatment. Median time to sputum smear and culture conversion was 90 (IQR 36-

173) and 89 (IQR 45-107) days, respectively (Table 5). In a multivariate Cox proportional hazard model, factors independently associated with faster time to culture conversion were HCV-negativity (HR 2.64, confidence interval (CI) 1.34-5.19; p=0.021), the absence of lung cavities (HR 4.56, CI 1.41-14.75; p=0.011) and higher serum albumin levels at treatment start (HR 1.09, CI 1.02-1.16; p=0.010). No association was found between prolonged bedaquiline treatment and time to culture conversion after adjustment (Table 6).

At the end of treatment, 36 of the 45 patients (80.0%) had favourable outcome. Nine (20.0%) had unfavourable outcome, including three deaths and one treatment failure with acquisition of resistance to bedaquiline. During post-treatment follow-up, one patient died before the 12-months endpoint and one died before the 24-months endpoint. No recurrences were recorded in the cohort (Table 5). The characteristics of patients who died or experienced treatment failure are summarised in Table 7.

With regard to causality assessment, bedaquiline was considered as unlikely related to all deaths and other serious adverse events.

Comparison of standard and prolonged bedaquiline treatment regimens

Overall, 12 (26.7%) and 33 patients (73.3%) received standard (median 183 days, IQR 168-185) and prolonged (median 418 days, IQR 292-665) bedaquiline treatment. Patients receiving prolonged bedaquiline treatment were more often previously treated for TB (p<0.001). They were more likely to have XDR-TB, bilateral lung involvement, cavitary TB and strains with resistance to a greater number of drugs, although these differences did not reach statistical significance (Supplementary Table 3). No significant differences were recorded between the two groups regarding the incidence of total, severe and serious adverse events, including liver enzyme elevation. No statistical difference was found in the rate of QTcF prolongation and >500ms values, nor in the maximum QTcF increase recorded during treatment (Table 4). Patients in the prolonged treatment group were more frequently sputum culture-positive at treatment start (p=0.048) and had slower time to culture conversion (91 versus 71 days, p=0.021) (Figure 2). Favourable and unfavourable treatment outcome rates at the end of treatment and during post-treatment follow-up were comparable between the two groups (Table 5).

DISCUSSION:

We report successful outcomes in 80% of MDR-TB patients treated with bedaquiline-containing regimens, with a high rate of adverse events.

This rate of success is remarkable, as our cohort included a substantial number of XDR-TB patients, HCV-infected cases, and intravenous drug abuser undergoing methadone treatment. Similar treatment outcomes are described in other high-resource settings, but these studies included fewer XDR-TB patients.[22-24] Previous studies including XDR-TB patients with low HIV-coinfection rates like in our cohort reported lower success rates.[25,26] Our results could be explained by multiple factors: treatment follow-up in specialised centres with comprehensive patient support and appropriate management of adverse events, free-of-charge treatment and social support for precarious populations, availability of reliable DST by a reference laboratory, and tailored treatment regimens including lung surgery.[27]

The duration of bedaquiline treatment was established according to individual clinical evaluation. Interestingly, no difference in terms of efficacy and tolerance was found between standard and prolonged bedaquiline groups, although the latter group arguably contained more difficult-to-treat patients who achieved delayed sputum culture conversion. Moreover, prolonged bedaquiline treatment courses could partly explain the better outcomes in our cohort with regards to bedaquiline-treatment arms of the published Phase II clinical trials.[7,8] Notably, almost all the patients in our cohort received linezolid, a drug shown to improve treatment outcomes of MDR-TB patients.[28,29] Other re-purposed drugs, such as clofazimine[30] and carbapenems[31-32] might have played a role. Finally, more than half of the patients received a last-generation fluoroquinolone, and 22% received high-dose moxifloxacin to overcome low-level fluoroquinolone resistance. A standardized nine-months treatment regimen including a fourth-generation fluoroquinolone at high dose showed to achieve good outcomes in patients harbouring strains with low-level fluoroquinolone resistance.[33]

Overall, 11% of patients were lost to follow-up during treatment, and this rate markedly increased during post-therapeutic follow-up. This finding is possibly related to the precarious state of the patients, who are in the vast majority foreign-born and often migrating to seek for adequate health care. The rate of loss to follow-up is similar to previous studies.[22-24] In our cohort, five patients died, three during treatment and two after the end of treatment. For the two patients who died during treatment after developing neurological complications (Patients 3 and 4, Table 7), causality assessment is challenging. The event was considered possibly related to linezolid because this drug has well-documented neurological toxicity;[28,29] and bedaquiline involvement was considered as unlikely but can't be excluded. The single treatment failure (Patient 1, Table 7) was linked to bedaquiline resistance during treatment with only three likely active drugs. There is a need for efficient drug companions to protect new drugs from acquired resistance, as recently illustrated by the case of a patient who developed sequential resistance to bedaquiline and delamanid.[34,35]

Lung surgery was performed in 26·7% of our patients, who had cavitary disease, to attain sustained culture conversion. The capacity of TB drugs to penetrate into lungs cavities and advanced tissue necrosis is unknown and should lead to consider surgical treatment.[36]

Toxicity is often a major issue in the long-term treatment needed for MDR-TB: in the placebo arm of the C208 study, 98% of participants experienced adverse events.[7] Observational cohorts corroborate the high frequency of side effects.[37] In our study, all patients except one experienced at least one adverse event, and 82% had to stop one drug because of side effects. More than half of our patients experienced peripheral neuropathy, a known complication of prolonged linezolid administration.[38] QTc prolongation in our cohort was more frequent than what has been reported in bedaquiline-treated patients in other studies,[7,8,10,11] possibly because many patients in our cohort received other QT-prolonging drugs, such as moxifloxacin, clofazimine, and other non-TB drugs like methadone. Indeed, the administration of both high-dose moxifloxacin and methadone was associated with >500 ms QTcF values in our cohort. No association was found between clofazimine treatment and QTc prolongation. However, studies with bigger sample size will be needed to confirm these results. There was no statistical difference in the number of total adverse events, serious adverse events, and severe adverse events between standard and prolonged bedaquiline groups. No difference was found in the incidence of bedaquiline-associated adverse events, such as liver enzyme elevation, pancreatitis and QTc prolongation. Although all episodes of >500 ms QTcF prolongation occurred in the prolonged bedaquiline group, most patients experienced the prolongation during the first six months of treatment. Median QTcF values remained stable during the whole treatment duration in the prolonged bedaquiline group, irrespective of the cumulative exposure to the drug. Notably, no patient in the cohort received both bedaquiline and delamanid, so no conclusion can be drawn on the tolerability of the association of these two drugs.[39,40]

Our study has multiple limitations. First, data were collected retrospectively, possibly leading to an increase in the rate of loss to follow-up patients and to underreporting of adverse events. Second, the small sample size of the cohort might not have enough power to show existing differences between the standard and prolonged bedaquiline groups. Third, no control group of patients not receiving bedaquiline was analysed. Finally, no measurement of bedaquiline levels in blood nor surgical specimens was performed in the study.

In conclusion, our results show promising outcomes in a cohort including mostly XDR-TB patients, and reassuring safety profile of prolonged bedaquiline administration. The prolongation of bedaquiline treatment in selected patients with multiple risk factors could have contributed to the high rate of favourable outcomes. We therefore advocate for extension of bedaquiline treatment beyond 24 weeks according to the individual patient's need and to predefined criteria (Table 1), as done for other TB drugs.

The advent of new drugs offers us the opportunity to both improve outcomes and reduce the toxicity of MDR/XDR-TB treatment. A rapid increase in the evidence supporting the use of bedaquiline will hopefully provide additional treatment options for these patients.

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Table 1. Criteria and pre-requisites for prolonged bedaquiline treatment which have been used in this cohort

Pre-requisites for bedaquiline prolongation beyond 24 weeks	**Definition**
Good tolerability	No serious side effects linked to bedaquiline during the first 24 weeks of treatment.
Informed consent	Patient should be correctly informed about the potential risks and benefits, as well as on the available evidence on prolonged bedaquiline treatment.
Closely monitored treatment	Treatment should be monitored closely according to available guidance for timely detection and management of adverse events.
Expert opinion by an independent organization	Expert opinion should be provided by an external organism (ie. national or international consilium).
Pharmacovigilance system	A proper pharmacovigilance system should be in place.
Criteria for bedaquiline prolongation beyond 24 weeks	**Definition**
Late microbiological response	Patient still sputum culture-positive after 3 months or more of treatment and not meeting the criteria for treatment failure
Insufficient number of effective drugs in the treatment regimen	Less than 4 effective drugs* left in the treatment regimen if bedaquiline is discontinued. The paucity of effective drugs in the treatment regimen may be due to drug resistance pattern, adverse events or any other contraindication.
Presence of risk factors for poor treatment outcome	Presence of risk factor for unfavourable treatment outcome, including: • Low BMI (<18.5 kg/m^2) • High sputum smear bacillary load (2+/3+) • HIV-positivity • Extensive / advanced pulmonary disease • Contraindication to surgery

* Effective drug = never used before in a failing regimen, susceptible according to a reliable DST result

Table 2. Socio-demographic characteristics, disease features and treatment regimens of the 45 patients

Categorical variables	**n (%)**
Sex, male	36 (80.0)
Foreign-born • Eastern Europe and Caucasus region • Africa • Asia	44 (97.8) 36 (80·0) 5 (11·1) 3 (6·7)
HIV infection	2 (4.4)
HCV infection	21 (46.7)
Intravenous drug use with methadone substitution	6 (13.3)
Pulmonary tuberculosis localization	44 (97.8)
Bilateral lung involvement (N=44)	36 (81.8)
Cavities on chest radiography (N=44)	39 (88.6)
Sputum smear-positive at treatment start	42 (93.3)
Sputum culture-positive at treatment start	41 (91.1)
Any previous tuberculosis treatment	34 (75.6)
Drugs contained in the treatment regimen	
Ethambutol	20 (44.4)
Pyrazinamide	19 (42.2)
Amikacin	32 (71.1)
Capreomycin	3 (6.7)
Moxifloxacin (400 mg / 800 mg daily)	14 (31.1) / 10 (22.2)
Levofloxacin (1000 mg daily)	8 (17.8)
Ethionamide	11 (24.4)
Para-amino salicylic acid	40 (88.9)
Cycloserine	32 (71.1)
Linezolid	43 (95.6)
Clofazimine	20 (44.4)
Imipenem / clavulanic acid	28 (62.2)
Meropenem / clavulanic acid	2 (4.4)
Continuous variables	**median (interquartile range)**
Age at admission (years)	38 (30 – 42)
Serum albumin (g/dl)	32.5 (27.5 – 36.9)
Body Mass Index (kg/m2)	19.6 (17.8 – 22.0)
N of drugs included in the treatment regimen	7 (6 – 8)

Fq: fluoroquinolones; SLI: second-line injectable drugs; DST: drug susceptibility testing.

Table 3. Baseline phenotypic and genotypic resistance pattern of the strains isolated from the 45 patients.

Antibiotic (gene)	Phenotypic resistance	Genotypic resistance
Rifampicin (*rpoB*)	45/45 (100)	45/45 (100)
Isoniazid (*inhA* promoter, *katG*)	45/45 (100)	45/45 (100)
Pyrazinamide (*pncA*)	17/19 (89.5)	32/45 (71.1)
Ethambutol (*embB*)	33/44 (75.0)	18/45 (40.0)
Streptomycin	41/45 (91.1)	n. d.
Amikacin (*rrs*)	14/45 (31.1)	12/45 (26.7)
Kanamycin (*rrs*)	28/45 (62.2)	12/45 (26.7)
Capreomycin (*rrs*)	17/45 (37.8)	12/45 (26.7)
Ofloxacin (*gyrA*, *gyrB*)	35/45 (77.8)	33/45 (73.3)
Moxifloxacin* (*gyrA*, *gyrB*)	24/45 (53.3)	33/45 (73.3)
Ethionamide (*inhA* promoter, *ethA*, *ethR*)	38/44 (86.4)	38/44 (86.4)
Para-amino salicylic acid	14/45 (31.1)	n.d.
Cycloserine	24/45 (54.5)	n.d.
Linezolid	0/45	n.d.
Bedaquiline	0/22	n. d.

Figures represent resistant strains / tested strains (%) for each drug. Sequenced genes and promoters are specified for each drug.

n.d. = not done

* Moxifloxacin was tested at 2 mg/L in order to distinguish between low and high-level resistance. Strains which were ofloxacin resistant but moxifloxacin susceptible were considered low-level resistant to moxifloxacin

Table 4. Treatment safety in the whole cohort and comparison between patients receiving standard (≤190 days) or prolonged (>190 days) bedaquiline treatment

Categorical variables, n (%)	Whole cohort (n=45)	Standard Bdq treatment (n=12)	Prolonged Bdq treatment (n=33)	p-value*
Any AE	44 (97.8)	12 (100)	32 (97.0)	1.000
Any severe AE	28 (62.2)	5 (41.7)	23 (69.7)	0.163
Any serious AE	7 (15.6)	1 (8.3)	6 (18.2)	0.655
At least one drug stopped due to AEs	37 (82.2)	8 (66.7)	29 (87.9)	0.181
Bedaquiline stopped due to AEs	3 (6.7)	1 (8.3)	2 (6.1)	1.000
Liver enzyme elevation	17 (37.8)	6 (50.0)	11 (33.3)	0.325
Pancreatitis	1 (2.2)	1 (8.3)	0	0.267
QTcF >500 ms	5 (11.1)	0	5 (15.2)	0.303
QTcF >60 ms increase	13 (28.9)	4 (33.3)	9 (27.3)	0.721
Continuous variables, median (interquartile range)	**Whole cohort (n=45)**	**Standard Bdq treatment (n=12)**	**Prolonged Bdq treatment (n=33)**	**p-value***
Maximum QTcF increase during treatment	36.2 (17.9 – 68.5)	31.9 (16.0 – 73.3)	41.6 (19.7 – 63.7)	0.437

AE = adverse event

* Comparison between patients with standard and prolonged bedaquiline treatment, calculated with the Wilcoxon's test for continuous variables and Fisher's exact test for categorical variables.

Table 5. Treatment outcomes of the whole cohort and comparison between patients receiving standard (≤190 days) or prolonged (>190 days) bedaquiline treatment

Categorical variables, n (%)	**Whole cohort (n=45)**	**Standard Bdq treatment (n=12)**	**Prolonged Bdq treatment (n=33)**	**p-value***
Favourable outcomes	36 (80.0)	9 (75.0)	27 (81.8)	0.682
- Cured	34 (75.6)	7 (58.3)	27 (81.8)	0.131
- Treatment completed	2 (4.4)	2 (16.7)	0	0.067
Unfavourable outcomes	9 (20.0)	3 (25.0)	6 (18.2)	1.000
- Lost to follow-up	5 (11.1)	2 (16.7)	3 (9.1)	0.598
- Died	3 (6.7)	1 (8.3)	2 (6.1)	1.000
- Treatment failed	1 (2.2)	0	1 (3.0)	1.000
Follow-up at 12 months	(n=36)**	(n=9)**	(n=27)**	
- No recurrence	23 (63.9)	4 (44.4)	19 (70.4)	0.235
- Lost to follow-up	9 (25.0)	5 (55.6)	4 (14.8)	0.026
- Died	1 (2.8)	0	1 (3.7)	1.000
- Censored	3 (8.3)	0	3 (11.1)	0.558
Follow-up at 24 months	(n=23)**	(n=4)**	(n=19)	
- No recurrence	4 (17.4)	1 (25.0)	3 (15.8)	1.000
- Lost to follow-up	2 (8.7)	0	2 (10.5)	1.000
- Died	1 (3.7)	1 (25.0)	0	0.174
- Censored	16 (69.6)	2 (50.0)	14 (73.7)	0.557
Continuous variables, median (interquartile range)	**Whole cohort (n=45)**	**Standard Bdq treatment (n=12)**	**Prolonged Bdq treatment (n=33)**	**p-value***
Time to sputum smear conversion	90 (36 – 173)	71 (22 – 90)	110 (47 – 195)	0.002
Time to sputum culture conversion	89 (45 - 107)	71 (53 – 88)	91 (43 – 114)	0.021

*Comparison between patients with standard and prolonged bedaquiline treatment, calculated with the Wilcoxon's test for continuous variables and Fisher's exact test for categorical variables.

**Patients eligible for follow-up are those with favourable outcomes at previous time point.

Table 6. Univariate and multivariate Cox proportional hazards models assessing the association of factors with time to culture conversion.

Variables	Univariate HR (95% C. I.)	P	Multivariate HR (95% C. I.)	p
Age		0.765		
Sex, male	0.54 (0.24-1.22)	0.159		0.611
HCV–negative	2.64 (1.34-5.19)	0.005	2.35 (1.14-4.88)	0.021
Serum albumin	1.11 (1.05-1.18)	<0.001	1.09 (1.02-1.16)	0.010
Body mass index		0.407		
Absence of lung cavities	5.35 (1.70-16.87)	0.014	4.56 (1.41-14.75)	0.011
Bilateral lung involvement	0.31 (0.13-0.73)	0.013		0.270
Sputum smear positive at treatment start	0.16 (0.02-1.34)	0.173		0.524
Treatment with ethambutol		0.400		
Treatment with pyrazinamide	0.52 (0.27-1.02)	0.051		0.424
Treatment with any second-line injectable		0.892		
Treatment with any fluoroquinolone	1.71 (0.89-3.29)	0.105		0.334
Treatment with ethionamide	2.09 (0.97-4.53)	0.077		0.051
Surgery		0.877		
Standard bedaquiline treatment duration	0.39 (0.17-0.89)	0.035		0.702

HR = hazard ratio; C. I. = confidence interval.

- **Table 7. Summary of the characteristics and evolution of patients who died or experienced treatment failure**

Patient	Outcome	TB diagnosis	Initial treatment regimen	Description
1	Treatment failure	Extended pulmonary XDR-TB	Bdq, Am, Eto, PAS, Lzd, Cfz	Lzd, PAS and Am had to be stopped because of peripheral neuropathy, gastrointestinal intolerance and hearing loss. After achieving initial culture conversion, the patient reverted to sputum culture positivity at 14 months of treatment, acquiring resistance to Bdq.
2	Death	Extended pulmonary MDR-TB	Am, Mfx, Cs, PAS, Lzd, Cfz	The patient died from dissemination of a pharyngolaryngeal cancer after 9 months of treatment. Bdq was started at month 4 and stopped at month 5 because of QTcF interval prolongation.
3	Death	Extended pulmonary XDR-TB	Bdq, Cs, PAS, Lzd, Ipm/Cln, Amx/Clv	The patient achieved sputum culture conversion at month 4 of treatment. Since month 15 of treatment, he developed peripheral neuropathy, difficulty to swallow, myositis, myoclonia, and psychiatric disorders. He died one month later with no obvious diagnosis. No signs of serotonin syndrome were present, and the patient did not receive any serotonin-inducing concomitant medication. Autopsy found no explanation for the death.
4	Death	Extended pulmonary XDR-TB	Bdq, Am, PAS, Lzd, Ipm/Cln, Amx/Clv	The patient achieved sputum culture conversion at month 4 of treatment, after performing lung surgery. From month 9 of treatment, he gradually developed peripheral neuropathy and neuro-psychiatric disorders. After a septic shock due to catheter infection at month 21, he was diagnosed with polyradiculoneuropathy and brainstem disorder. He died few days later. No signs of serotonin syndrome were present, and the patient did not receive any serotonin-inducing concomitant medication. Autopsy was not performed.
5	Death (during follow-up)	Extended pulmonary XDR-TB	Bdq, Cm, Mfx, Cfz, Lzd, Ipm/Cln, Amx/Clv	The patient underwent lung surgery at month 1, and was declared cured after 19 months of treatment. He died of overdose of recreational drugs one month after the end of treatment.

6	Death (during follow-up)	Extended pulmonary XDR-TB	Bdq, E, Z, Am, Mfx, PAS, Lzd	The patient suffered from type-1 diabetes and chronic renal insufficiency. He was declared cured after 18 months of treatment, and had no sign of recurrence He died of terminal renal failure 20 months after the end of treatment.
Bdq=bedaquiline; E=ethambutol, Z=pyrazinamide, Am=amikacin; Cm=capreomycin; Mfx=moxifloxacin; Eto=ethionamide; Cs=cycloserine, PAS=para-aminosalicylic acid; Lzd=linezolid, Cfz=clofazimine; Ipm/Cln=imipenem/cilastatin; Amx/Clv=amoxicilline/clavulanic acid.				

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Authors contributions:

L.G. made a substantial contribution to the conception and design of the work, to the acquisition, analysis and interpretation of data, performed statistical analysis, wrote the manuscript, critically revised the manuscript, and gave final approval of the current version to be published. M.J. and M.F.-J. made a substantial contribution to the conception and design of the work, to the acquisition, analysis and interpretation of data, wrote the manuscript, critically revised the manuscript, and gave final approval of the current version to be published. D.L.D. made a substantial contribution to the conception and design of the work, to the acquisition, analysis and interpretation of data, critically revised the manuscript, and gave final approval of the current version to be published. M.L., D.M.O., C.B., N.V., J.R., Y.Y., and E.C. made a contribution to the acquisition of the data, critically revised the manuscript, and gave final approval of the current version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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