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Effectiveness and safety of bedaquiline-containing regimens in the treatment of multidrug and extensively drug-resistant tuberculosis: a multicentre study.

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Summary (200/200 words)

Large studies on bedaquiline used programmatically to treat multidrug-resistant (MDR-) and extensively drug-resistant tuberculosis (XDR-TB) are lacking. The study aim is to evaluate effectiveness and safety of bedaquiline-containing regimens in a large retrospective, observational study conducted in 25 centres and 15 countries in all continents.

428 MDR-TB cases were analysed (61.5% males; 22.1% HIV-positive, 45.6% XDR-TB). MDR-TB cases were admitted to hospital for 179 days (92-280) and exposed to bedaquiline for 168 days (86-180). Treatment regimens included linezolid, moxifloxacin and carbapenems (82.0%, 58.4%, and 15.3% of cases, respectively).

Sputum smear and culture conversion rates in MDR-TB cases were 63.6 and 30.1% at 30 days, 81.1 and 56.7% at 60 days; 85.5 and 80.5% at 90 days and 90.9 and 91.8%, respectively at the end of treatment. The time to smear and culture conversion was 34 (30-60) and 60 (33-90) days.

Out of 247 culture-confirmed MDR-TB cases completing treatment, 71.3% achieved success (62.4% cured; 8.9% completed treatment), 13.4% died, 7.3% defaulted, 7.7% failed.

Twenty-seven rifampicin-resistant cases were also described.

Bedaquiline was interrupted due to adverse events in 5.8% of cases. A single case died having electrocardiographic abnormalities probably non-bedaquiline related.

Bedaquiline-containing regimens achieved high conversion and success rates under programmatic conditions.

Introduction

A total of 480,000 cases of multidrug-resistant tuberculosis (MDR-TB) and 100,000 of rifampicin-resistant (RR)-TB eligible for MDR-TB treatment were estimated by the World Health Organization (WHO) to have occurred in 2015, with 190,000 deaths [1]. Over half of the estimated MDR-TB cases occurred in India, China, Russian Federation, and the other Former Soviet Union countries, as well as in South Africa [1]. Globally, about 10% of the MDR-TB strains meet the criteria defining XDR-TB (resistance to any fluoroquinolone and at least one second-line injectable drug) [1,2].

Treatment for M/XDR-TB is long, expensive, and characterised by a high rate of adverse events [3-19]. The main difficulty is the identification of at least four active drugs to design an effective regimen [3,4,7,8, 12-15].
The previous stepwise approach based on the hierarchical use of first- and second-line anti-TB drugs classified into five groups has been recently modified by WHO. The new classification includes 4 groups of drugs (A: fluoroquinolones; B: second-line injectable agents; C: other core second-line agents and D: add-on agents, subdivided into the sub-groups D1, D2 and D3) [7,12].

Two newly available drugs, delamanid, [16-18] and bedaquiline [19-25], together with some re-purposed drugs (linezolid [13,26-32], carbapenems [33-38] and clofazimine [39] among others [40-43]) are presently pivotal in ongoing scientific discussions.
The information available today on bedaquiline is still limited to phase 2 studies in relatively small cohorts treated under clinical trials conditions, the largest study not exceeding 233 patients [19-24]. In particular, at this present time, no study of size informs us on the effectiveness, safety, and tolerability of bedaquiline, in different continents and programmatic conditions.

Given the concerns around the adverse events of bedaquiline (particularly QT-prolongation, potentially at highest risk when added to fluoroquinolones – moxifloxacin, levofloxacin, oflofloxacin-, clofazimine, delamanid and methadone amongst others), additional evidence on its safety, apart from that provided by the registration trials, is urgently needed [44-46].

Recently, TB reference centres belonging to the International Bedaquiline Study Group (IBSG, a network merging the centres belonging to the International Carbapenems Study Group-ICSG [36-38] and the ERS/ALAT and Brazilian Society collaborative projects [47,48] coordinated by the

ERS TB Collaborating Centre) conducted an observational study on the therapeutic contribution of bedaquiline added to a background regimen (as per WHO guidelines) when treating MDR- and XDR-TB cases.

The aim of the present study is to evaluate the effectiveness, safety, and tolerability of bedaquiline within optimised background regimens in a large multi-centre cohort of MDR- and XDR-TB patients treated under programmatic conditions.

Material and Methods

The methodological approach adopted for this study is similar to that described in previous ICSG studies [36-38]. Twenty-five MDR-TB reference centres located in 15 countries in Africa, Asia, Europe, Oceania and Southern America (Argentina, Australia, Belarus, Belgium, Greece, India, Italy, Netherlands, Peru, Portugal, Russian Federation, South Africa, Spain, Sweden, and United Kingdom) retrospectively recruited RR- and culture-confirmed MDR-TB patients aged ≥15 years. An MDR-TB case was defined as an individual with TB disease caused by M. tuberculosis strains phenotypically resistant to at least isoniazid and rifampicin. RR-TB cases were those diagnosed through Xpert MTB/RIF® (Cepheid, Sunnyvale USA) complemented by line probe assays. XDR-TB cases were those whose disease was due to MDR M. tuberculosis strains with additional resistance to any fluoroquinolone and one of the second-line injectable drugs (i.e., amikacin, capreomycin, and kanamycin) [1,8].

Patients starting their treatment between January 1st 2008 and August 30th 2016 were consecutively enrolled based on their exposure to bedaquiline during the intensive and the continuation phase. Bedaquiline was made accessible either under compassionate use, within the expanded access programmes or purchased by respective countries.

An individualised TB regimen was administered following the results of the drug susceptibility test (DST) carried out by externally quality-assured laboratories [36-38]. RR cases were managed according to the national guidelines in force in their respective countries (South Africa) [49]. Physicians were free to prescribe the accompanying anti-TB treatment to obtain the best possible regimen in their setting and, consequently, no specific protocol or method beyond local guidelines was followed.

Bedaquiline was administered at the recommended dosage of 400 mg once a day for 14 days then 200 mg three times a week for 22 weeks.

A standardized ad-hoc e-form was used to collect epidemiological (i.e., age, place of birth and residence, gender, migrant status from a TB high-incidence country), clinical (i.e., cardiac and

thyroid disorders, HIV-testing, HIV-infection status, administration of HIV drugs, previous TB diagnosis and treatment, previous treatment outcomes, radiological findings, TB therapy and related adverse events, duration of exposure to bedaquiline, delamanid, linezolid, carbapenems, adjuvant surgery, sputum smear and culture positivity at the baseline, and during treatment-at 30, 60, and 90 days-, time to sputum smear and culture conversion, WHO treatment outcomes, duration of hospital stay), and microbiological (i.e., DST results) data from medical records.

The ethical approval for the retrospective collection of clinical data was obtained by the coordinating centre.

Culture-confirmed MDR- and RR-TB cases were analysed separately. MDR- and XDR-TB cases' outcomes were compared by setting.

Qualitative and quantitative variables were summarised with percentages and medians (interquartile ranges –IQR). Chi-square or Fisher exact and Mann-Whitney tests were used to statistically compare qualitative and quantitative variables, respectively.

A p-value of less than 0.05 was considered statistically significant. Statistical computations were performed with Stata 13.0 (StataCorp, College Station, TX).

Results

Demographic, epidemiological and clinical characteristics of the patients are summarised in Table 1, treatment outcome results in Table 2-3 and safety and tolerability information on bedaquiline in Table 4.

A total of 455 MDR- and RR-TB patients were recruited: 428 (94.1%) and 27 (5.9%) were diagnosed by conventional culture and DST and by Xpert and line-probe assays, respectively.

Male (271, 59.6%) was the most prevalent gender in the cohort (263, 61.5%, VS. 8, 29.6%, in the MDR- and RR-TB groups, respectively; p= 0.001), and the median (IQR) age was 35 (27-44) years (35, 27-44, VS. 31, 24-40, for MDR- and RR-TB groups, respectively; p= 0.16).

The characteristics of the 428 culture-confirmed MDR-TB patients are summarised in Table 1. Migrants from high to low TB incidence countries were 45 (10.5%).

The proportion of HIV co-infected patients was 22.1%; their median (IQR) CD4 cell count was 269/mmc (168-470) and the majority (92, 97.9%) received antiretroviral therapy.

Pulmonary TB was diagnosed in 426 out of 428 (99.5%) cases, the extra-pulmonary locations being abdominal and the nervous system (2). The percentages of sputum smear and culture positive cases were 72.1% and 98.4%, respectively.

Less than half were affected by XDR-TB (195/428, 45.6%), with a median (IQR) number of drug resistances of 3 (1-5). Overall, 334/428 (78.0%) cases were previously treated for TB.

The prevalence of drug resistance was as follows: streptomycin 185 (94.4%), pyrazinamide 145 (70.4%), fluoroquinolones 267 (64.5%), amikacin 131 (44.4%), capreomycin 127 (41.6%), kanamycin 179 (59.3%), ethionamide 135 (59.7%), PAS 70 (35.7%), linezolid 4 (10.5%), ethambutol 186 (77.5%), and cycloserine 20 (12.3%).

Treatment regimens included linezolid (82.0%), clofazimine (52.6%), moxifloxacin (58.4%), second-line injectables (45.8%) and carbapenems (15.3%).

Patients were exposed to bedaquiline for a median (IQR) of 168 (86-180) days (Table 4). Five (1.2%) patients underwent treatment with both delamanid and bedaquiline. Adjuvant surgical therapy was performed in 55 (13%) cases.

The median (IQR range) treatment duration in the cohort was 18 (10-22) months.

Sputum smear and culture conversion rates were 63.6% and 30.1% at 30 days; 81.1% and 56.7% at 60 days; 85.5% and 80.5% at 90 days, and 90.0% and 91.8%, at the end of treatment (for those completing it) respectively. The median (IQR) time to sputum smear and culture conversion was 34 (30-60) and 60 (33-90) days (Figure 1).

Out of 247 culture-confirmed MDR-TB cases completing treatment, 71.3% achieved success (62.4% cured and 8.9% completed treatment), 13.4% died, 7.3% defaulted, and 7.7% failed.

Sputum smear and culture conversion rates at the end of treatment were not significantly different among XDR- and MDR-TB cases (p=0.73 and 0.96, respectively).

The treatment success rates were higher in Eastern Europe and in settings other than in Africa (Table 3), including both MDR- and XDR-TB patients. The HIV co-infection prevalence in Africa, Eastern Europe and remaining settings together was 88/190 (46.3%), 0/150 (0%) and 6/85 (7.1%), respectively.

Figure 2 summarises the median values of the QTcF interval (QT interval in the electrocardiogram corrected according to Fredericia formula) and its temporal trends in the cohort.

Adverse events potentially attributed to bedaquiline were reported in 80 of 413 (19.4%) cases where this information was provided (Table 4). The majority of the adverse events described were represented by nausea, peripheral neuropathy, and otovestibular toxicity.
In particular, 51 of 428 (11.9%) patients discontinued bedaquiline (25 or 5.8% -reporting adverse events), of these 26 (51%) did so permanently.
Although we do not have the exact information on how many cases interrupted bedaquiline due to QTcF increase, 24 of 247 (9.7%) experienced QTcF prolongation >500msec.
One patient was started on bedaquiline with a baseline QTcF of 553 msec, which then decreased to 536 at week 4 and 554 at week 8. A second patient, with a baseline QTcF of 352 msec, had a transient increase (510 at week 3) and then a decline (358 at week 4): the clinician reported the cause of death was not heart-related.
The median (IQR) exposure to bedaquiline amongst the 26 patients who permanently interrupted was 69 (27.5-135) days, and 85.5 (44.3-160) days in those 33 patients who died.
Out of 33 who died, we have QT information on 21 (63.6%), no patient had a baseline QT >500 msec.

We have information of a single patient who died having ECG disturbances. The patient after 131 days of bedaquiline exposure had PVC (premature ventricular contraction) bigeminy and fatal cardiac arrest. Interestingly, the QT was below the 'alert' threshold: 414 msec at baseline (QTcF: 438), with a maximum value of 462 at week 6 (QTcF: 462) then decreasing to 356 (QTcF: 398) at week 16.

Furthermore, 104 out of 348 (29.9%) cases treated with linezolid reported adverse events attributed to this drug; 16/58 (27.6%) of them (for whom final treatment data was available) permanently discontinued linezolid.

Discussion

The aim of the present study was to retrospectively evaluate the safety, tolerability, and effectiveness of bedaquiline-containing regimens in a large observational cohort of MDR- and XDR-TB patients treated under programmatic conditions.

The results of our study demonstrate that, overall, bedaquiline-containing regimens achieve a relatively higher proportion of treatment success with a relatively lower proportion of adverse events within different settings than previously described.

Of note, culture conversion rates were higher than those reported in cohorts with an analogous degree of disease severity; with time to sputum smear and culture conversion identical or earlier to those observed in comparable cohorts; the proportion of treatment success was higher, and the percentage of adverse outcomes (death, failure) lower than those seen in available study cohorts with the matching disease severity; adverse events due to bedaquiline requiring interruption of the drug were relatively uncommon (5.8%) [14,15].

This is, to our knowledge, the largest study describing effectiveness, safety, and tolerability of bedaquiline within optimised background regimens (almost double the size of the largest one published so far) and the first one in the scientific literature reporting on the programmatic use of bedaquiline for the treatment of M/XDR-TB patients on 5 continents.

Regarding effectiveness, although difficult to attribute to bedaquiline given the causality of the results observed, we can report that bedaquiline-containing regimens achieved culture conversion rates exceeding 90% at the end of treatment and treatment success >70%, higher than those observed in other MDR-TB cohorts [3,4,19,21].

In comparison with Menzies' data on Individual Patient Data analysis (where there was a 43% success in XDR), in our bedaquiline treated XDR-TB cohort the success rate was 71.3% [3,4].

In a phase 2 double blind, randomised control trial study by Diacon et al. [20] the median time to culture conversion in 79 bedaquiline-treated MDR-TB patients was 83 days; this compares with our median time of 60 days. In the study by Diacon et al. the culture conversion at the end of 24 weeks was 79% and at 120 weeks was 58% VS. 91.7% at the end of therapy in our study, and the cure rates 58% and 62,4%, respectively [20].

Pym et al. conducted a phase 2 trial to assess safety and efficacy of bedaquiliine in 233 patients, culture conversion was seen in 72.2% at 120 weeks, 8.6% of patients discontinued treatment and 6.9% of patients died [19].

Regarding safety, in the Diacon's study [20] 13% of patients in the bedaquiline group died (10 of 79 VS. 2 of 81 in the placebo group) versus 33 (13.4%) out of the 247 who had an evaluable outcome in our cohort.

The most frequent adverse events in our study were nausea (31.5%), otovestibular toxicity (23.3%), peripheral neuropathy (23.3%), vomiting (21.2%) and arthralgia (20.4%), their frequencies being slightly lower than those described during Diacon et al's licensing study with 41% nausea, 29% vomiting and 37% arthralgia [21]. Importantly, in the Diacon's study the proportion of the adverse events was similar in the group VS. placebo patients, suggesting they were probably due to the background regimen.

In this context, other second-line drugs like fluoroquinolones or clofazimine might contribute to cardiologic or other adverse events [14,15,39] and invite caution and ECG monitoring.

Our study confirms that bedaquiline-containing regimens are effective, as demonstrated by the fact that a sizeable number of patients were treated with salvage regimens due to previous treatment failure, unfavourable resistance profile, toxicity, or all three.

The larger group of patients in real programmatic conditions around the globe reinforces previous findings that bedaquiline is well tolerated and adverse events are less common than previously thought.

Enthusiasm over bedaquiline and delamanid has been curtailed following concerns of potential cardiotoxicity. Both new drugs are associated with QT prolongation, which may lead to arrhythmia and sudden death, a major reason why their association has not been recommended. Moreover, the new drugs are likely to be associated with a fluoroquinolone and clofazimine, both known to prolong QT intervals. Our results appear to show that the risk is probably lower than previously known, although the specific role of the many drugs with QT prolonging potential (and their summation or synergistic effect) still needs to be fully understood.

QT prolongation occurred in 9.7% of patients. However, interruption of bedaquiline due to AEs, occurred in 25 (5.8%) patients.

According to the information available, a single case out of 33 who died had ECG abnormalities, although the QT was below the 500 msec threshold and a single QTcF measurement was above 450 but below 500 msec. The revision of clinical and ECG history of the patient makes relationship between bedaquiline use and fatal arrhythmia unlikely.

Although information on QT is available in 64% of cases, and the timing of their assessment not standardised, it seems the majority of cases died for non heart-related reasons.

Close monitoring of drug safety should be implemented widely, particularly for rare adverse events. A comprehensive, population-level pharmacological surveillance in the post-marketing phase might allow a better assessment of the safety and tolerability profile of bedaquiline, alone or in combination with other potentially cardio-toxic anti-TB drugs.

We underline the importance of using, in future studies, a standardised ECG monitoring protocol allowing to exclude inter- and intra-day variability in QTc measurements. For study purposes 24 hour Holter monitoring is probably the best strategy to assess the true impact of drugs on QTc. This is clearly not feasible under programmatic conditions.

The strengths of the study are the large sized cohort, the inclusion of cases from several countries (ranging from 10% of all patients receiving bedaquiline in South Africa to 100% of bedaquiline-

treated patients in Argentina, Greece, Portugal and Spain), and the detailed information collected from the participating centres. The large sample size allows, for the first time, to compare treatment outcomes from different settings.

Some variables, like the drug-resistance patterns, the number of previous anti-treatment cycles and the HIV sero-prevalence varied among the settings participating in the study.

However, the observational and retrospective design of the study has inbuilt limitations (recent guideline changes, different resource settings, different standards of care, dataset differences) so that the study findings need to be confirmed by larger randomised controlled clinical trials. The different operating procedures adopted in different settings, as well as the heterogeneous drug resistance patterns, could underestimate the real benefits of the bedaquiline-containing regimens.

However, the new information provided by this observational study allows clinicians managing difficult-to-treat TB cases in programmatic conditions to better understand how to use bedaquiline in case the minimum number of active drugs necessary to design an effective regimen is lacking [1,8,15].

Although new compounds will hopefully appear soon to support the move towards TB Elimination [50], bedaquiline confirms to have potential given its ‘core drug’ characteristics [12] to manage MDR- and XDR-TB cases even in field conditions, and eventually to be used in newly designed anti-TB regimens of the future.

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Table 1. Demographic, epidemiological, and clinical characteristics of 428 culture-confirmed multidrug-resistant tuberculosis patients exposed to bedaquiline-containing regimens.

Variables		
Median (IQR) age		35 (27-44)
Male, n (%)		263 (61.5)
Median (IQR) body weight at admission, kg		56 (47-65)
Median (IQR) height, cm		169 (160-176)
Migrant, n (%)		45 (10.5)
Employed, n (%)		110 (26.6)
Prisoner, n (%)		23 (5.6)
Pregnant, n (%)		1 (0.75)
Thyroid disease, n (%)		12 (2.9)
Heart disease, n (%)		40 (12.6)
Pre-existing ECG abnormality, n (%)		13 (4.1)
Alcoholism, n (%)		132 (36.4)
Drug abuse, n (%)		75 (18.2)
Methadone use, n (%)		0 (0.0)
Diabetes, n (%)		26 (6.3)
HIV infection testing, n (%)		425 (99.3)
HIV-positive, n (%)		94 (22.1)
Median (IQR) CD4 count at baseline, mmc		269 (168-470)
Median (IQR) nadir CD4+ cell counts, mmc		222 (160-402)
Anti-retroviral therapy exposure, n (%)		92 (97.9)
Prior anti-TB therapy, n (%)		334 (78.0)
Median (IQR) n times treated >1 month		2 (1-2)
Prior TB treatment outcome, n (%)	*Success*	68 (25.9)
	Cured	41 (15.6)
	Completed	27 (10.3)
	Defaulted	35 (13.3)
	Transferred out	20 (7.6)
	Failed	140 (53.2)
Pulmonary surgery, n (%)		55 (13.0)
Previous MDR-TB, n (%)		169 (53.3)
Pulmonary involvement, n (%)		426(99.5)
Extra-pulmonary involvement, n (%)		11 (2.6)
Radiology involvement, n (%)	*Cavitary lesion*	81 (24.5)
	Bilateral pulmonary involvement with cavitary lesions	147 (44.4)
	Bilateral pulmonary involvement	56 (16.9)
	Noncavitary nonbilateral pulmonary	47 (14.2)

Sputum-smear positive, n (%)	305 (72.1)
Sputum culture positive, n (%)	421 (98.4)
Resistance to streptomycin, n (%)	185 (94.4)
Resistance to ethambutol, n (%)	186 (77.5)
Resistance to pyrazinamide, n (%)	145 (70.4)
Resistance to fluoroqinolones, n (%)	267 (64.5)
Resistance to amikacin, n (%)	131 (44.4)
Resistance to capreomycin, n (%)	127 (41.6)
Resistance to kanamycin, n (%)	179 (59.3)
Resistance to ethionamide, n (%)	135 (59.7)
Resistance to cycloserine, n (%)	20 (12.3)
Resistance to para-aminosalicylic acid, n (%)	70 (35.7)
Resistance to linezolid, n (%)	4 (10.5)
Resistance to rifabutin, n (%)	32 (91.4)
XDR-TB, n (%)	195 (45.6)
MDR/XDR-TB contacts, n (%)	105 (25.6)
Median (IQR) hospital stay	179 (92-280)

IQR: interquartile range; XDR-TB: extensively drug-resistant tuberculosis; MDR: multidrug-resistant

Table 2. Treatment outcome and conversion rates of 428 culture-confirmed multidrug-resistant tuberculosis patients exposed to bedaquiline-containing regimens.

Variables		
Sputum smear conversion 30 days, n (%)		206 (63.6)
Sputum culture conversion 30 days, n (%)		117 (30.1)
Sputum smear conversion 60 days, n (%)		257 (81.1)
Sputum culture conversion 60 days, n (%)		213 (56.7)
Sputum smear conversion 90 days, n (%)		265 (85.5)
Sputum culture conversion 90 days, n (%)		298 (80.5)
Sputum smear conversion at the end of treatment, n (%)		126 (90.0)
Sputum culture conversion at the end of treatment, n (%)		191 (91.8)
Median (IQR) time to sputum smear conversion, days		34 (30-60)
Median (IQR) time to sputum culture conversion, days		60 (33-90)
Treatment outcome, n (%)	*Success*	176 (71.3)
	Cured	154 (62.4)
	Completed	22 (8.9)
	Died	33 (13.4)
	Defaulted	18 (7.3)
	Failure	19 (7.7)
	Transferred out	1 (0.4)
Median (IQR) months of treatment after MDR-TB diagnosis		18 (10-22)
Mean (SD) body weight at the end of treatment, kg		61.9 (13.9)

IQR: interquartile range; MDR-TB: multidrug-resistant tuberculosis; SD: standard deviation

Table 3. Treatment outcomes of 428 culture-confirmed MDR- and XDR-TB patients exposed to bedaquiline-containing regimens in different settings.

Treatment outcome	Africa (n=113)	Eastern Europe (n=85)	Other settings (n=49)	p-value
Total cohort				
Treatment success	73 (64.6)	65 (76.5)	38 (77.6)	0.10
Cured	73 (64.6)	54 (63.5)	27 (55.1)	<0.0001
Completed	-	11 (12.9)	11 (22.5)	
Died	27 (23.9)	3 (3.5)	3 (6.1)	
Defaulted	9 (8.0)	8 (9.4)	1 (2.0)	
Failure	3 (2.7)	9 (10.6)	7 (14.3)	
Transferred out	1 (0.9)	-	-	
MDR-TB				
Treatment success	36 (58.1)	28 (71.8)	22 (81.5)	0.07
Cured	36 (58.1)	20 (51.3)	11 (40.7)	<0.0001
Completed	-	8 (20.5)	11 (40.7)	
Died	17 (27.4)	3 (7.7)	1 (3.7)	
Defaulted	7 (11.3)	3 (7.7)	1 (3.7)	
Failure	1 (1.6)	5 (12.8)	3 (11.1)	
Transferred out	1 (1.6)	-	-	
XDR-TB				
Treatment success	37 (72.6)	37 (80.4)	16 (72.7)	0.63
Cured	37 (72.6)	34 (73.9)	16 (72.7)	0.006
Completed	-	3 (6.5)	-	
Died	10 (19.6)	-	2 (9.1)	
Defaulted	2 (3.9)	5 (10.9)	-	
Failure	2 (3.9)	4 (8.7)	4 (18.2)	
Transferred out	-	-	-	

MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis

Table 4. Safety and tolerability profile of bedaquiline-containing regimens in a cohort of 428 culture-confirmed MDR-TB patients.

Interruption of bedaquiline, n (%)	51 (11.9)
Interruption of bedaquiline due to adverse events, n (%)	25 (5.8)
Adverse events presumably due to bedaquiline, n (%)	80 (19.4)
Bedaquiline restarted if interrupted, n (%)	25 (49)
Median (IQR) total bedaquiline exposure, days	168 (86-180)
Creatinine >1.4x ULN, n (%)	91 (22.1)
Lipase >1.6x ULN, n (%)	1 (0.4)
ALT >3x ULN, n (%)	92 (22.3)
Bilirubin >2x ULN, n (%)	47 (11.4)
Median (IQR) albumin, gr/dl	36 (30-40)
Potassium <3.4 or >5.6 mmol/L, n (%)	98 (23.8)
Magnesium <0.59 mmol/L, n (%)	21 (10.6)
Calcium <1.75 mmol/L, n (%)	23 (7.6)
Nausea, n (%)	130 (31.5)
Neuropathy peripheral, n (%)	96 (23.3)
Oto-vestibular toxicity, n (%)	96 (23.3)
Vomiting, n (%)	87 (21.2)
Anaemia, n (%)	86 (20.9)
Arthralgia, n (%)	84 (20.4)
Skin rash, n (%)	63 (15.3)
Pancreatitis, n (%)	4 (1.3)
Diarrhoea, n (%)	56 (13.6)
Renal failure, n (%)	47 (11.4)
Thrombocytopenia, n (%)	41 (9.9)
Neutropenia, n (%)	40 (9.7)
Lymphocytopenia, n (%)	40 (9.7)
QT prolongation, n (%)	24 (9.7)
Hypothyroidism, n (%)	38 (9.3)
Psychiatric disorder, n (%)	29 (7.0)
Tendinopathy, n (%)	18 (4.4)
Optic neuropathy, n (%)	10 (2.4)
Deep vein thrombosis, n (%)	7 (1.7)
Hallucinations, n (%)	2 (0.5)
Stroke, n (%)	1 (0.3)

Figure 1. Sputum smear and culture conversion rates of 428 culture-confirmed multidrug-resistant tuberculosis patients exposed to bedaquiline-containing regimens.

Figure 2. Median values of the QTcF interval and its temporal trends in the cohort in the initial 12 weeks of treatment

Median values

	Baseline	**Week 4**	**Week 8**	**Week 12**
Median (IQR) QTcF, msec	401.5 (372.0-437.0)	424.0 (395.0-456.0)	430.0 (401.0-450.0)	425.5 (389.0-449.0)

Temporal trends

The coloured dots indicate outlier patients
IQR: interquartile range; QTcF: QT interval in the electrocardiogram corrected according to Fredericia formula

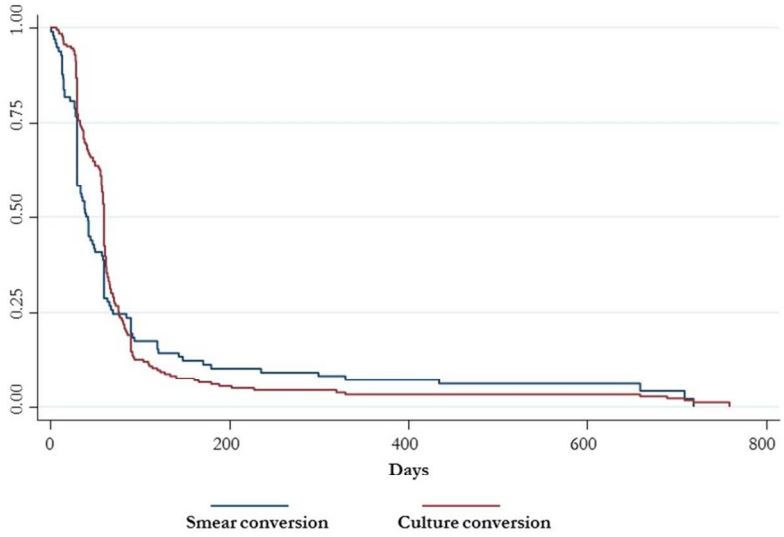

Figure 1. Sputum smear and culture conversion rates of 428 culture-confirmed multidrug-resistant tuberculosis patients exposed to bedaquiline-containing regimens.
Figure 1
205x119mm (150 x 150 DPI)

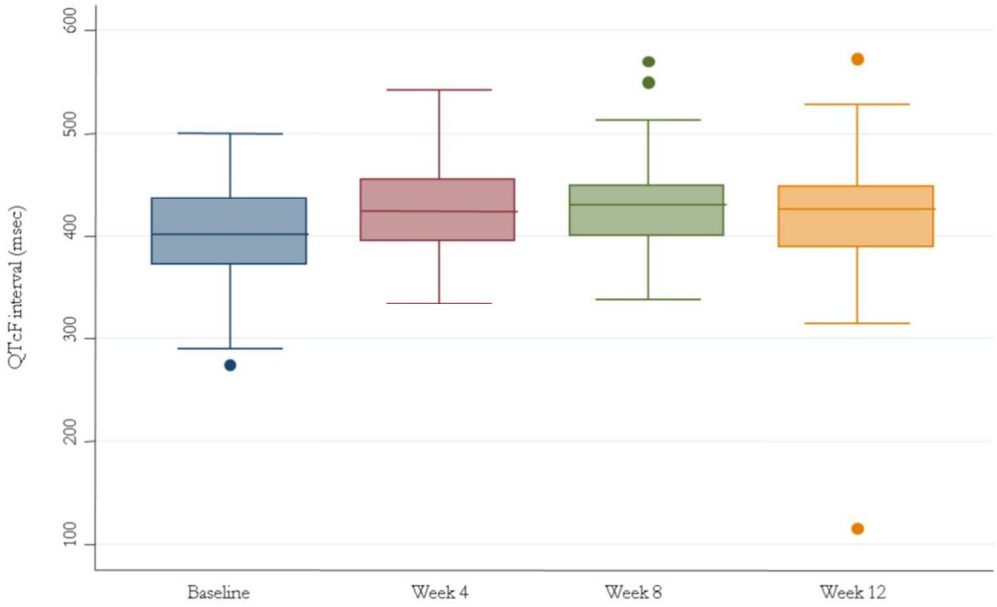

Figure 2. Median values of the QTcF interval and its temporal trends in the cohort in the initial 12 weeks of treatment
Figure 2
235x148mm (125 x 125 DPI)