Combined treatment of drug-resistant tuberculosis with bedaquiline and delamanid: a systematic review

To the Editors:

The World Health Organization (WHO) estimated that 490 000 cases of multidrug-resistant (MDR) tuberculosis (TB) (defined as TB caused by *Mycobacterium tuberculosis* strains resistant to at least isoniazid and rifampicin) occurred in 2016. Among them, ~6.2% had extensively drug-resistant (XDR) TB (*i.e.* TB caused by MDR strains with additional resistance to fluoroquinolones and at least one second-line injectable drug) [1].

An appropriate pharmacological regimen can bacteriologically and clinically cure, and prevent the emergence and spread of further resistances. However, the management of MDR- and other chronic TB cases can be clinically challenging, as well as raise public health concerns, in patients with limited treatment options. An insufficient number of active drugs during both intensive and continuation phases cannot allow the patient to be saved, while creating further resistance [2].

Due to this reason, to date, the overall success rate for MDR-TB is less than 60%, and is lower than 40% for XDR-TB [1].

Furthermore, the incidence of adverse events can be particularly high when administering anti-MDR-TB drugs [2–6].

The recent availability of bedaquiline and delamanid could positively affect poor treatment outcomes of MDR-TB cases, reduce the occurrence of adverse events, and halt further drug resistance and transmission.

Bedaquiline is effective and safe, even if increased QT interval and cardiac complications have been recorded [3–7].

Delamanid-containing regimens can achieve treatment success in up to 80% of MDR/XDR-TB cases, with limited adverse events, such as prolonged QT interval and emesis [4, 8].

The WHO does not recommend combination of bedaquiline and delamanid. owing to a potential high risk of cardiac toxicity [9]; however, in difficult-to-treat MDR/XDR-TB cases, where pharmacological alternatives to design a regimen with four active drugs are not available, bedaquiline and delamanid combined treatment, in addition to optimised background regimen, was proposed as a life-saving option [10, 11].

The aim of the present study was to perform a systematic review on the efficacy and safety of co-administered bedaquiline and delamanid in MDR-TB patients.

Peer-reviewed articles written in English reporting on efficacy/effectiveness, safety, and tolerability of individualised regimens containing both bedaquiline and delamanid in patients with culture- and drug susceptibility testing (DST)-confirmed MDR/XDR-TB were selected.

PubMed and Embase were used to identify any relevant manuscripts published up until May 8, 2018, excluding editorials, reviews, experimental studies on animal models, manuscripts describing TB patients recruited without a confirmed bacteriological diagnosis, and conference abstracts (because of limited available information).

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TABLE 1 Summary of the findings in six studies reporting on delamanid and bedaquiline combination treatment to manage 87 multidrug-resistant (MDR)/extensively drug-resistant (XDR) tuberculosis (TB) cases

First author, publication year	Countries	Patients n (% HIV+)	Pre-treated for TB	MDR-TB cases	XDR-TB cases	Use of the two drugs	Concomitant QTc prolonging drugs	Patients taking one or both drugs for more than 24 weeks	Median exposure to BDQ/DLM combination treatment	BDQ and/or DLM discontinuations	QTc	Sputum culture conversion	Outcome/ evaluable outcome
Lachâtre [11], 2016	France	1 (0%)	1 (100%)	0	1 (100%)	0 sequential 1 (100%) concomitant	None	Not specified	Not specified	0 for non-cardiac adverse events 0 for cardiac adverse events	0 with >60 ms increase 0 with >500 ms	Not specified	Favourable outcome (but not further specified)
Maryandishev [12], 2017	India, Russian Federation, the Netherlands	5 (0%)	5 (100%)	0	5 (100%)	0 sequential 5 (100%) concomitant	3 patients CFZ (60%) 1 patient MFX (20%) 1 patient CFZ + MFX (20%)	1 (20%)	168 days (range 155–427)	0 for non-cardiac adverse events 0 for cardiac adverse events	>60 ms increase not reported 2 with >500 ms (520 ms at week 16 in one patient; 509 ms at weeks 5 and 9 in one patient)	3/5 (60%)	1 cured 3 culture converted 1 died (respiratory insufficiency)
Guglielmetti [13], 2018	France, Latvia	10 (0%)	Information not available	4 MDR + FLQs resistant (40%)	6 (60%)	4 (40%) sequential (BDQ followed by DLM) because of BDQ resistance 6 (60%) concomitant	3 patients CFZ (30%) 1 patient MFX (10%) 4 patients CFZ + MFX (40%)	6 (60%) BDQ (average 391 days) 9 (90%) DLM (average 532 days)	171 days (IQR 138–327)	0 for non-cardiac adverse events 0 for cardiac adverse events	0 with >60 ms increase 2 with >500 ms (both reverted after discontinuation of a companion drug, CFZ and MFX, respectively)	8/8 (100%)	9 cured 1 lost to follow up (last culture negative)
Mohr [8], 2018	South Africa	32 (some, but not specified)	Information not available	Not specified: all patients were RR-TB and beyond	Not specified: all patients were RR-TB and beyond	Information not available	24 patients CFZ (75%)	Occurred, but it was not specified	168 days (estimated from the text, but not specified)	Not clearly specified for non-cardiac adverse events 0 for cardiac adverse events	6 with >60 ms increase (5 also receiving CFZ) 0 with >500 ms	Not specified	Not specified
Ferlazzo [14], 2018	Armenia, South Africa, India	28 (39%)	Not specified	2 MDR (7%) 2 MDR + INJ (7%) 10 MDR + FLQs resistant (36%)	14 (50%)	0 sequential 28 (100%) concomitant	17 patients CFZ (61%) 4 MFX (14%) 2 CFZ + MFX (7%)	Occurred, but it was not specified	168 days (estimated from the text, but not specified)	0 for non-cardiac adverse events 0 for cardiac adverse events	4 with >60 ms increase 0 with >500 ms	17/23 (74%)	22 culture negative 2 culture positive 1 unable to produce sputum 1 unclassified (only one sputum culture negative) 1 lost to follow up (while culture positive) 1 died
Kim [15], 2018	South Korea	11 (39%)	11 (100%)	7 (63.6%)	4 (36.4%)	9 sequential, BDQ followed by DLM 1 sequential, DLM followed by BDQ 1 concomitant	3 FLQs (37%) 6 CFZ (54.5%)	Occurred, but it was not specified	168 days	0 for non-cardiac adverse events 2 (18.2%) for cardiac adverse events; one case: concomitant use; one case: DLM-BDQ sequential use (QTc normalised after discontinuation)	9 (81.8%) significant prolongation#; all patients had at least one QTc value >460 msec	7/7 (100%)	All 7 who were culture positive had culture conversion
Total (range 2016–2018)		87 (15/55, 27.3%)	17/17 (100%)	25/55 (45.5%)	30/55 (54.5%)	14/55 sequential (25.5%) 41/55 concomitant (74.5%)		10/15 (66.7%)	Range (median values) 168–171 days	0/87 for non-cardiac adverse events 2/87 (2.3%) for cardiac adverse events	23/87 (26.4%)	35/43 (81.4%)	10/14 cured (71.4%)

#: absolute value >450 ms in men or >470 ms in women (8 cases), or as a >60 ms increase from baseline (3 cases). BDQ: bedaquiline; DLM: delamanid; FLQs: fluoroquinolones; RR: rifampin-resistant; INJ: injectables; CFZ: clofazimine; MFX: moxifloxacin; IQR: interquartile range.

The keywords TB, delamanid and bedaquiline were used in different combinations. Two authors independently performed the search and evaluated titles and abstracts. The following variables were collected in suitable manuscripts: sputum smear and culture conversion, treatment outcomes, type of adverse events and their severity, demographics, mycobacterial drug resistance patterns, treatment regimens and their duration. The study was conducted following the 2009 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement.

Out of the 126 identified articles, 119 were excluded because they did not report any information on the combined clinical use of the two drugs.

Seven studies [8, 10–15] met the inclusion criteria (one patient [10] was also described in the manuscript by Maryandyshev *et al.* [12] with additional information and, therefore, was counted only once in this review): two letters [11, 13] and four articles [8, 12, 14, 15] published between 2016 and 2018 have been included.

Overall, 87 adult cases were treated with delamanid and bedaquiline in Armenia, France, India, Latvia, Russian Federation, South Africa, South Korea and the Netherlands. DST results and HIV status were available in only 55/87 cases. More than half of those (30/55, 54.5%) had XDR-TB [11–14] and 27.3% (15/55) were HIV co-infected (with information available). All the cases with information provided on previous treatment (17/17) were re-treatment cases (table 1) [11, 12, 15].

Bedaquiline and delamanid were prescribed concomitantly and sequentially in 41/55 (74.5%) and 14/55 cases, respectively [11–15]; one study did not specify (table 1) [8].

In sequential use, delamanid was started in 13 cases following the discontinuation of bedaquiline (range 1 −79 days); in one case only bedaquiline was started following the discontinuation of delamanid (1 day after). [13, 15]. In 10 out of 15 cases with information on this variable (66.7%) bedaquiline and/or delamanid were prescribed for more than the recommended 24 weeks (6 months). In all cohorts, other QT-prolonging drugs were employed together with bedaquiline and/or delamanid (*e.g.* clofazimine and/or fluoroquinolones).

Out of 87 patients, 23 (26.4%) showed >1 episode of QT prolongation >450 ms in men or 470 ms in women, or a QT increase >60 ms from baseline values. However, only 2/87 (2.3%) interrupted bedaquiline and/or delamanid for cardiac adverse events. The other adverse events reported in the various studies were rarely attributed to bedaquiline, delamanid or both [8, 13–15]. Nevertheless, in most cases there were several confounding factors, such as co-administered anti-TB drugs and comorbidities, which make univocal attribution questionable [15].

Treatment outcomes were generally favourable considering the severity of these cases: sputum culture conversion was observed in the large majority of patients (81.4%; 35/43 of those with available information) and a 71.4% success rate (cured patients: 10/14 with information available) was obtained.

Details of the studies (adverse events and treatment outcomes) are summarised in table 1.

We systematically reviewed the available scientific evidence on the combined use of bedaquiline and delamanid in the management of MDR/XDR-TB cases.

Missing data could be found for four of the six studies that were not specifically designed to study safety and efficacy of bedaquiline and delamanid-containing regimens.

The main conclusions are the following:

1) Combined treatment is increasingly used to treat cases with intolerances, XDR-TB patients or other chronic patients with limited treatment options. Selection of this combination for each patient occurred in most cases after consultation of and approval by an “ad hoc” national/international committee (National or International TB Consilia) [8, 11–15], while only a minority of cases were prescribed the two drugs exclusively by local clinicians (15 patients before September 2016).
2) The majority of patients were concomitantly treated with bedaquiline and delamanid, and a significant proportion of them were prescribed one or both drugs for >6 months.
3) Bedaquiline has a half-life of 5.5 months, in contrast with delamanid, which has a shorter half-life (38 h), leading to a potential co-administration when delamanid is prescribed sequentially after bedaquiline [15]. Evidence on additive or synergistic QT prolonging effects is lacking.
4) Only 2.3% interrupted for the occurrence of life-threatening cardiac adverse events [7].
5) Sputum culture conversion rate after 6 months of treatment was considerably higher (81.4%) than historical MDR/XDR-TB patient cohorts [1].

6) Although the majority of patients are still on treatment, the 71.4% success rate found in the cases completing treatment is encouraging for future difficult-to-treat patients.
7) No published information is presently available on the combined use of delamanid and bedaquiline in children.

Due to the limited number of studies and patients evaluated, and relative information incompleteness, results should be evaluated cautiously. Well-designed experimental studies are imminently needed. However, reported data suggest that under specific conditions (*e.g.* quality-controlled laboratory, clinical expertise, monitoring capacity, support by TB consilia), combined treatment with bedaquiline and delamanid could be promising in chronic TB patients with limited therapeutic options.

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