Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence

Emanuele Pontali[1,5], Giovanni Sotgiu[2,5], Lia D'Ambrosio[3,4], Rosella Centis[3] and Giovanni Battista Migliori[3]

Affiliations: [1]Dept of Infectious Diseases, Galliera Hospital, Genova, Italy. [2]Clinical Epidemiology and Medical Statistics Unit, Dept of Biomedical Sciences - University of Sassari – Research, Medical Education and Professional Development Unit, AOU Sassari, Sassari, Italy. [3]WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy. [4]Public Health Consulting Group, Lugano, Switzerland. [5]Both authors contributed equally.

Correspondence: Giovanni Battista Migliori, WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, via Roncaccio 16, 21049 Tradate, Italy.
E-mail: giovannibattista.migliori@fsm.it

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Systematic review of the available scientific evidence on the role of bedaquiline in new effective M/XDR-TB regimens http://ow.ly/V68ZF

The importance of adequately managing multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) cases for TB control and elimination are underlined in the new World Health Organization (WHO) "End TB Strategy" [1, 2] as part of pillar one (integrated, patient-centred care and prevention; element 2: treatment of all people with TB including drug-resistant TB, and patient support) and in the recently published "Framework towards TB elimination in low incidence countries" in its priority action 5 (optimise the prevention and care of drug-resistant TB) and the related background documents [3–5]. Furthermore, both in the End TB Strategy (pillar 3: intensified research and innovation) and in the Framework towards TB elimination in low incidence countries (priority action 7: invest in research and new tools) the need for new anti-TB drugs is strongly emphasised [1, 3, 6]. The reasons why new anti-TB drugs are needed are rather obvious if you look closely at the dimensions of the MDR-TB epidemic and the treatment successes achieved so far.

Out of the 480 000 MDR-TB cases estimated by WHO to have occurred in 2014, only 123 000 (one quarter) have been diagnosed and notified [1]. Overall, 3.3% of new and 20% of retreatment cases harbour MDR-TB resistant strains of *Mycobacterium tuberculosis*, of whom 9.7% are proven to be XDR-TB [1]. The country with the highest prevalence of MDR-TB cases is Belarus (34% in new and 69% in retreatment cases), where 29% of the cases are reported to be XDR-TB [1, 7].

Treatment of MDR-TB and XDR-TB has proven, so far, to be long, expensive and difficult-to-manage, and unfortunately, its outcomes are suboptimal in most cohorts [8, 9]. Although XDR-TB cases actually represent a relatively small proportion of all MDR-TB cases (9%), their treatment and management are significantly more challenging both for clinicians and national programmes [1]. Globally, treatment success of MDR-TB cases in the 2012 cohort was 50% (16% died, 16% were lost to follow-up, 10% failed, and 8% had no outcome information). Among the cases with a resistance pattern beyond XDR-TB the proportion of treatment success is unfortunately as low as 20%, with 49% failure and death [8, 10].

The design of an effective regimen to treat MDR- and XDR-TB is based on the stepwise use of second-line TB drugs whose choice needs to be guided by drug susceptibility testing (DST) [11–13]. Unfortunately, at the programmatic level neither the drugs needed nor the specific DST to test them are always available

[11–13]. Furthermore, the possibility of combining second-line drugs to design the best possible regimen is often affected by a number of significant adverse events, which negatively affect adherence to treatment [14, 15].

During the past few years new drugs to treat MDR/XDR-TB have been developed following trials and, given their initial (although incomplete) efficacy data, they have received provisional approval while additional registration trials are still ongoing [16, 17]. The updated pipeline of new drugs is reported in figure 1 [1].

Although more is now known about the efficacy and tolerability of linezolid [18–25] and interest has been recently raised by the possibility of using other re-proposed compounds (carbapenems [26–28], sulphonamides [29, 30], and mefloquine [31], among others), the new anti-TB drugs delamanid [32] and bedaquiline are particularly promising [33–35].

The *European Respiratory Journal (ERJ)* has recently published several contributions related to the compassionate use of bedaquiline [36, 37] and the delamanid compassionate programme based on the European Respiratory Society (ERS)/WHO TB Consilium [38–45]. To better understand the role of bedaquiline in new regimens for the future we systematically reviewed the scientific evidence available on this drug.

Using the search engine PubMed the key words bedaquiline and efficacy/effectiveness were used to retrieve post-marketing studies describing the outcome of bedaquiline-containing regimens. Strict selection criteria, excluding case-reports and case-series, letters, editorials, and commentaries were adopted. No temporal ranges (until November 1, 2015) or language restrictions were included in the search. A total of 216 records were retrieved. Apart from less than 10 case-series/reports (including an interim cohort analysis on TB/HIV co-infected persons), no post-marketing experimental studies have been published, until now, to assess its effectiveness profile in the general population after the pre-marketing trials. The search results, which include the new study by PYM *et al.* [46] are summarised in table 1.

In this issue of the *ERJ*, PYM *et al.* [46] report results from the TMC207-C209 study. This study was a phase 2, multicentre, open-label, single-arm trial (TMC207-C209; ClinicalTrials.gov identifier: NCT00910871), conducted to confirm the safety and efficacy of bedaquiline. The trial enrolled 233 patients (63.5% with MDR-TB, 18.9% with pre-XDR-TB, and 16.3% with XDR-TB). Most of them (87.1%) had already received second-line drugs during previous treatment(s). In terms of efficacy, PYM *et al.* [46] observed that culture conversion at 24 weeks was durable and associated with a high likelihood of response at 120 weeks. Final culture conversion at 120 weeks was 72.2%, with decreasing rates when resistance patterns worsened, *i.e.* 73.1%, 70.5% and 62.2% in MDR-TB, pre-XDR-TB and XDR-TB cases, respectively.

When considering safety, the most common adverse events were those typically observed during MDR-TB treatment. In addition, only six (2.6%) subjects discontinued bedaquiline before week 24 due to adverse
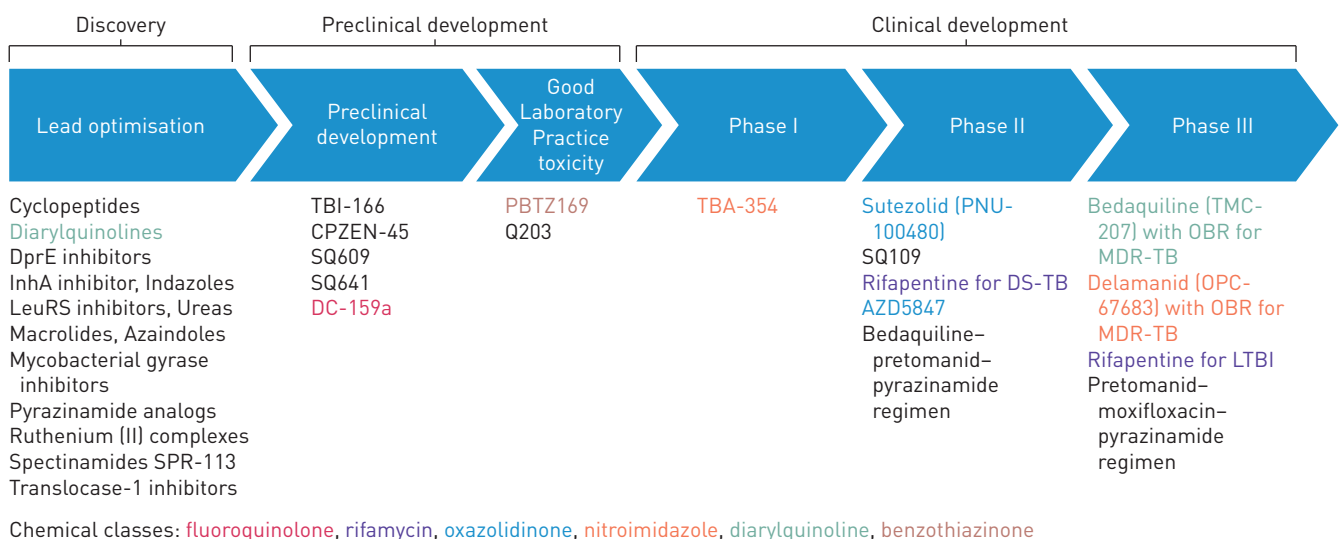

Discovery	Preclinical development		Clinical development		
Lead optimisation	**Preclinical development**	**Good Laboratory Practice toxicity**	**Phase I**	**Phase II**	**Phase III**
Cyclopeptides	TBI-166	PBTZ169	TBA-354	Sutezolid (PNU-100480)	Bedaquiline (TMC-207) with OBR for MDR-TB
Diarylquinolines	CPZEN-45	Q203		SQ109	Delamanid (OPC-67683) with OBR for MDR-TB
DprE inhibitors	SQ609			Rifapentine for DS-TB	
InhA inhibitor, Indazoles	SQ641			AZD5847	Rifapentine for LTBI
LeuRS inhibitors, Ureas	DC-159a			Bedaquiline– pretomanid– pyrazinamide regimen	Pretomanid– moxifloxacin– pyrazinamide regimen
Macrolides, Azaindoles					
Mycobacterial gyrase inhibitors					
Pyrazinamide analogs					
Ruthenium (II) complexes					
Spectinamides SPR-113					
Translocase-1 inhibitors					

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

FIGURE 1 The development pipeline for new tuberculosis drugs in August 2015. Details of the projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php. OBR: optimised background regimen; DprE: decaprenylphosphoryl-β-D-ribose2'-epimerase; InhA: inhibin alpha; LeuRS: leucyl-tRNA synthetase; MDR-TB: multidrug-resistant tuberculosis; DS-TB: drug-susceptible tuberculosis; LTBI: latent tuberculosis infection. Reproduced from [1] with permission from the publisher.

TABLE 1 Clinical studies on bedaquiline

First author [ref.], year	Type of study	Study number	Subjects taking bedaquiline n	Efficacy findings	Tolerability findings	QTc effect	Notes
DIACON [52], 2009	Phase IIb, randomised, multicentre, double-blind, placebo-controlled study	C208 stage 1	23	Bedaquiline reduced the time to conversion to a negative sputum culture. Bedaquiline increased the proportion of patients with conversion of sputum culture	Most AEs were mild to moderate; only nausea occurred significantly more frequently in the bedaquiline group	QT interval prolongation was observed in the bedaquiline and placebo group (more pronounced in the bedaquiline group), with intergroup differences ranging from 1.0 to 10.8 ms (p>0.05). None of the absolute values for the corrected QT interval exceeded 500 ms, and no adverse events were associated with ECG changes	
DIACON [53], 2014	Phase IIb, randomised, multicentre, double-blind, placebo-controlled study	C208 stage 2	79	Bedaquiline reduced the median time to culture conversion from 125 days to 83 days	Bedaquiline had similar rates of AEs, treatment-related AEs, and AEs leading to study discontinuation than placebo. The most frequent AEs were nausea, arthralgia and vomiting. The severity of most adverse events was grade 1 or 2	At study week 24, the mean change from baseline in the QTcF was an increase of 15.4 ms in the bedaquiline group and an increase of 3.3 ms in the placebo group (p<0.001). After bedaquiline treatment ended, the QTcF gradually decreased, and the mean value was similar to that in the placebo group by study week 60	
GUGLIELMETTI [58], 2015	Retrospective cohort study		35	Culture conversion rate was 97% after 6 months of therapy	Mild liver enzyme elevation (⩾2-fold from baseline) was reported in 14% of patients, and a ⩾5-fold increase occurred in two additional patients (6%). Confounding effect of concomitant drugs was mentioned	QTc prolongation was greater in individuals exposed to bedaquiline and fluoroquinolones, or clofazimine	
NDJEKA [59], 2015	Interim cohort analysis		91 (54 HIV⁺)	In total, 48 (76%) out of 63 patients with 6 months of follow-up either achieved culture conversion or remained culture-negative 6 months after initiation of bedaquiline	Good profile	Clofazimine use and not HIV infection was associated with QTc increase	ART based on either lopinavir/ ritonavir or nevirapine

TABLE 1 Continued

First author [ref.], year	Type of study	Study number	Subjects taking bedaquiline n	Efficacy findings	Tolerability findings	QTc effect	Notes
Pym [46], 2015	Phase 2, multicentre, multinational, open-label, noncomparative, single-arm trial	C209, NCT00910871	233	Culture conversion was 72.2% at 120 weeks, and 73.1%, 70.5% and 62.2% in MDR-TB, pre-XDR-TB and XDR-TB patients, respectively	The commonest AEs were similar to those generally reported in MDR-TB treatment cohorts; most were grade 1 or 2 Hyperuricaemia and increased aspartate aminotransferase were the most frequent grade ⩾3 AEs The incidence of AEs was highest during the first 12 weeks Serious AEs were reported in 47 (20.2%) patients: respiratory infections/disorders were the most common	Prolongation of the QTcF interval was reported infrequently Two patients had an increase in QTcF interval >500 ms; they were both taking clofazimine, and one had concurrent hypokalaemia No episodes of clinically significant dysrhythmia were reported	Two deaths were considered doubtfully related to bedaquiline

AEs: adverse events; QT interval: measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; QTc: QT interval corrected; QTcF: QT interval corrected by Fridericia's formula; MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

events or events related to the MDR-TB disease; discontinuations of the background regimen were more frequent. It has to be underscored that only two patients had clinically significant QTcF prolongation (>500 ms): one of them was in the bedaquiline arm, while both were prescribed clofazimine (which has known cardiotoxicity); one patient reported hypokalaemia. A significant mortality rate was observed (16 (6.9%) deaths), although only three deaths occurred during bedaquiline treatment (one attributed to renal impairment and two to advanced TB). As noted elsewhere, the investigators had to go more in depth to evaluate specific causes of death and death-related risk factors [47]. The most frequent cause of death was TB or related-illnesses, and 10 out of 16 dead patients never achieved sputum smear and culture conversion. After revision of the causes of death of all patients, none of those who died had presented QTcF prolongation >500 ms or had grade 3 or 4 liver adverse events (*i.e.* liver failure or an increase in liver function tests at levels more than 3 times the upper normal level).

Bedaquiline: mechanism of action

Bedaquiline is a novel compound (previously called TMC207 and R207910) belonging to the diarylquinoline group (figure 2). It was developed by Janssen Pharmaceuticals (Titusville, NJ, USA) [48]. This new anti-TB drug is the first in its class and presents a quinolinic central heterocyclic nucleus with alcohol and amine side chains responsible for its antimycobacterial activity. It is the only anti-TB drug that targets the energy metabolism of mycobacteria, inhibiting the mycobacterial ATP synthase [48, 49]. Bedaquiline is not active exclusively against drug-resistant *M. tuberculosis* isolates, but also against drug-susceptible strains. Its effective half-life is >24 h. [48].

Bedaquiline has been granted accelerated or conditional approval in the USA (2012) and Europe (2014) for use in MDR-TB, with interim guidance for its use provided by WHO [46, 50].

The trials

Initially a dose-finding study was carried out to investigate the early bactericidal activity, safety, tolerability and pharmacokinetics of bedaquiline [51]. Subsequently, the phase II C208 trial focusing on MDR-TB enrolled 47 patients that were randomly assigned to either placebo or bedaquiline [52]. A higher culture conversion rate was observed among those exposed to bedaquiline. The second stage of the same study (C208 stage 2) was a Phase IIb, randomised, multicentre double-blind, placebo-controlled study that involved 160 subjects [53]. A significant reduction in the time of sputum smear and culture conversion among those treated with bedaquiline was noted.

Steps for programmatic introduction

The introduction of bedaquiline for the treatment of drug-resistant TB in a new country usually precedes the "standard regulatory registration". It can occur through a number of alternative or complementary mechanisms [54–57].
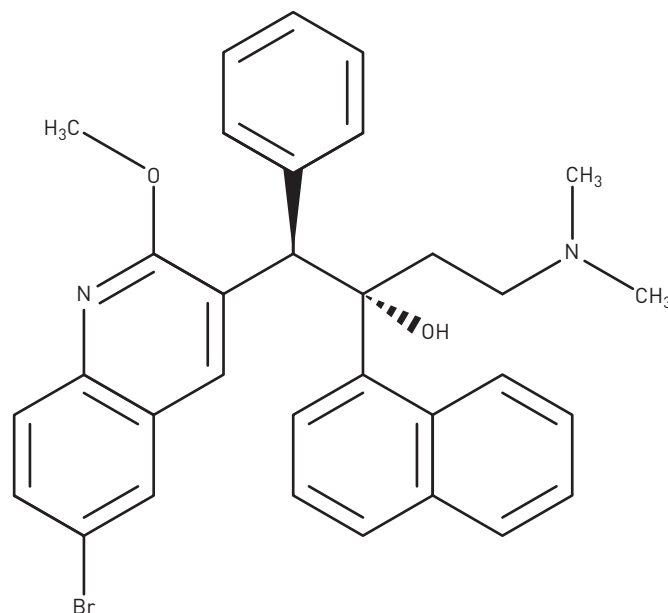

FIGURE 2 The molecular structure of bedaquiline.

- Compassionate use, managed through international programmes, is either a manufacturer-initiated or a donor-led initiative. This mechanism lasts until the manufacturer submits a registration file and the local authorities allow a temporary registration, or until an expanded access programme is started.
- Expanded access programmes are regulated programmes providing the drug to a larger population, but still in a restricted way. Several conditions usually have to be met by the prescribing centres requesting the drugs and patient selection should follow specific rules. This lasts until the programme is completed (if a maximum number of treatments have been scheduled) or until the drug is finally registered.
- Temporary registration allows prescription by designated specialised clinical centres, but the drug is available in the country and it is reimbursable by local health authorities or by health insurance. During this phase further studies are conducted to assess efficacy and safety of the drug. In addition, pharmacovigilance is in place locally to identify potentially as yet unrecognised adverse events early.

Open issues

Safety and tolerability

The most frequent adverse drug reactions (*i.e.* those observed in >10% of patients) during treatment with bedaquiline in the controlled trials were nausea, arthralgia and headache. Nevertheless, two key issues related to safety and tolerability remain open, and only additional data, such as those reported in this issue of the *ERJ,* will provide clarity on these issues [53].

The first issue is the increased risk of death reported in the bedaquiline treatment group (nine (11.4%) out of 79) compared with the placebo treatment group (two (2.5%) out of 81) in one of the studies based on the 120-week visit window [53]. This reported imbalance in deaths is still unexplained, and was not confirmed in the subsequent trials [46, 58, 59].

The second issue is the QTc prolongation. In the first studies the QT increase from baseline in the bedaquiline group persisted even after the drug was discontinued. In addition, co-administration of bedaquiline and drugs causing QTc prolongation (*e.g.* fluoroquinolones and clofazimine) showed an additional effect in most studies [58–60]. Based on this argument WHO has not, so far, recommended the co-administration of bedaquiline and delamanid [6, 45, 61]. Actually, their introduction and (eventually) co-administration should occur following the WHO recommendations and having met specific criteria [45]. In fact, WHO recommend that the new drugs bedaquiline and delamanid are prescribed within sound TB control programmes within optimised background regimens designed as per WHO guidelines, at the right dosages, with a pharmacovigilance system in place, obtaining the patient's informed consent and implementing proper monitoring (*i.e.* monitoring of the QT interval, specifically for bedaquiline) [50, 61, 62]. Among the criteria proposed for co-administration in sporadic cases the most relevant ones are probably: the impossibility of otherwise designing an effective treatment regimen; the treatment centre is at least nationally qualified; informed consent is available; pharmacovigilance is in place; and the choice to prescribe both the new drugs together is supported by expert opinion [45].

Resistance and drug susceptibility testing

Resistance to bedaquiline might occur. A mutant *atpE* gene seems to be responsible for such resistance [63]. In the study by PYM *et al.* [46] all 12 patients who had a post-baseline ≥4-fold increase in bedaquiline minimal inhibitory concentration had mutations in Rv0678, a transcriptional repressor of the MmpS5-MmpL5 efflux pump [46, 48]. Recently, this novel efflux mechanism of resistance has been identified to be responsible for low-level resistance to bedaquiline and clofazimine [48, 64, 65]. Unfortunately, to date, an adequate protocol to test bedaquiline susceptibility has not been developed and agreed upon [34, 35].

Paediatric use

A few studies on bedaquiline have already been completed leading to its approval in adults only [46, 52, 53]. Thus, at present, if an additional active drug is absolutely needed to treat a child affected by MDR/XDR-TB, bedaquiline can be employed on a case-by-case basis only if an effective regimen cannot otherwise be constructed [66].

A paediatric phase II, open-label, multicentre study has been planned and it should involve young subjects (0–18 years old) with confirmed or probable pulmonary MDR-TB to assess the pharmacokinetics of bedaquiline in combination with the background regimen (ClinicalTrials.gov identifier: NCT02354014).

Conclusions

Bedaquiline is a new and interesting drug for the treatment of MDR-TB and XDR-TB. New evidence suggests that tolerability is better than expected and the reported effect on the QT interval can be properly managed in specialised centres.

In perspective, bedaquiline might be used in new effective regimens for the treatment of MDR/XDR-TB, which will not include rifampicin and isoniazid (the two drugs defining MDR-TB). This will (hopefully) allow treatment of both drug-susceptible and drug-resistant cases with the same regimen. Furthermore, in absence of any negative interactions between antiretrovirals and rifamycins, these new regimens will allow easier management of HIV co-infected individuals. Bedaquiline is also a candidate component of shortened regimens for MDR-TB treatment [67]. In fact, with the purpose of finding responses to the challenges posed by MDR-TB treatment, the International Union Against Tuberculosis and Lung Disease has partnered with the Medical Research Council Clinical Trials Unit at University College London to evaluate shortened treatment regimens for MDR-TB and, in the second phase of the study, bedaquiline has been included to test shorter regimens [67, 68]. In addition, in order to favour access to bedaquiline and other new anti-TB drugs in developing countries, in 2014, the UNITAID International Drug Purchasing Facility with finance from Partners in Health (USA) launched a project aimed at treating 3200 MDR-TB patients with regimens that also include new anti-TB drugs over the following 4 years [69].

The issue of the possible combined use of delamanid and bedaquiline, currently not recommended by WHO [45, 50, 61], needs further evidence to protect patients from potential adverse events related to the combination of the two new drugs in addition to that deriving from the drugs used in the background regimen. Possible criteria to be taken into consideration to guide further studies on this have been recently described [45].

Furthermore, the potential of bedaquiline to possibily treat latent TB infection might deserve attention in the future [70].

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