Multidrug-resistant tuberculosis and beyond: an updated analysis of the current evidence on bedaquiline

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Bedaquiline is effective in managing MDR- and XDR-TB. Evidence indicates its tolerability and safety profile are good http://ow.ly/mWSz308QrVP

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Introduction

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) continue to be challenging at both the patient and programme level. The World Health Organization (WHO) estimated 480 000 new cases of MDR-TB in 2015 and an additional 100 000 cases diagnosed with rifampicin-resistant TB (RR-TB). India, China and the Russian Federation accounted for almost half (45%) of the total burden [1]. Out of 580 000 patients eligible for MDR-TB treatment, only 125 000 (20%) were enrolled in treatment programmes [1].

Unfortunately, MDR-TB treatment outcomes are still suboptimal; for example, 52% success rate in a 2013 cohort [1], which did not discriminate between MDR- (cases resistant to rifampicin and isonizazid), pre-XDR- (additional resistance to either a fluoroquinolone or a second-line injectable drug), XDR- (MDR-TB with additional resistance to both fluoroquinolones and injectables) and "beyond XDR-TB" patients, where success rates were <20% [2, 3].

Clinicians managing patients with MDR- and XDR-TB are well aware of the duration, expenses and complications (due to the frequently observed adverse events) involved in treating these cases in the absence of new drugs [2–7]. The main difficulty is, in fact, to identify at least four active drugs necessary to design an effective regimen [2–7].

New opportunities can be offered by the new drugs delamanid and bedaquiline, as well as by other repurposed drugs such as linezolid, carbapenems and clofazimine [8–22].

The *European Respiratory Journal*, which is committed to publishing important articles on TB and TB elimination [23, 24], has put together a special issue on the occasion of the World TB Day 2017, aimed at presenting new guidelines and an update on bedaquiline.

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The updated WHO MDR-TB guidelines

National TB programmes face difficulties in capturing the rapid changes presently observed in terms of treatment strategies, anti-TB drugs, novel combinations of anti-TB drugs, changes in duration of treatment, reclassification of anti-TB drugs, *etc.* without adequate guidance.

WHO is committed to broadening the access to MDR-TB care [25, 26].

In this issue of the journal, Falzon *et al.* [5] summarise the key elements of the new WHO Guidelines on MDR-TB treatment:

1) A second-line treatment is recommended for all RR-TB patients, regardless of whether isoniazid resistance of the mycobacterial isolate is confirmed;
2) A shorter MDR-TB treatment regimen is conditionally recommended for MDR/RR-TB patients, under specific eligibility criteria;
3) Recommendations for the treatment of children with MDR/RR-TB are based on the first-ever individual paediatric patient data meta-analysis on treatment outcomes;
4) MDR-TB medicines are now differently re-grouped, based on updated information about their efficacy and safety. In particular, clofazimine and linezolid are now recommended as core second-line MDR-TB drugs, while *p*-aminosalicylic acid has been moved to the list of add-on agents. Clarithromycin and other macrolides are no longer included for the treatment of MDR/RR-TB. Delamanid may also be used in patients aged 6–17 years old;
5) An evidence-informed recommendation on partial resection lung surgery is now included.

Importantly, the recommendation on "shorter" MDR-TB treatment regimen offers an effective, 9–12-month therapy to eligible patients, whose standardisation facilitates logistics and reduces direct and indirect costs [5].

The scientific debate is presently focused on the proportion of suitable patients in some geographical settings and on the impact on the MDR-TB epidemic [27–32].

Bedaquiline

This present editorial is also aimed at systematically summarising the evidence on bedaquiline, thereby updating the work carried out in 2016 [7].

Using the search engine PubMed, the key word "bedaquiline" was used to retrieve post-marketing studies describing the outcome of bedaquiline-containing regimens published between January 1, 2016 and December 31, 2016. A total of 93 records were retrieved. We evaluated them to identify those clinically relevant (n=67), and 52 papers were excluded on account of being editorials, reviews or commentaries. Of the remaining 15 papers, five were duplications, and finally, only 10 were selected. In addition, we included the papers published in this issue of the journal.

The evidence of the studies published in 2016 seems to confirm that bedaquiline is safe and effective (table 1).

In a recent paper, Guglielmetti *et al.* [33] compared MDR-TB regimens based on fluoroquinoles or bedaquiline, showing that the culture conversion rate was similar after 6 months of therapy. These findings should be carefully evaluated, as bedaquiline-treated patients were affected by more severe forms of TB (*e.g.* bilateral pulmonary involvement and number of susceptible drugs) [33].

In this issue of the ERJ, Udwadia *et al.* [34] describe the compassionate use of bedaquiline in India. Culture conversion was achieved in more than two-thirds of the patients exposed to bedaquiline, including a large proportion of XDR-TB cases. Bedaquiline was well tolerated and the QTcF intervals (*i.e.* QT interval in the electrocardiogram corrected according to Fridericia formula) increased by a mean of 49 ms, which was attributable to the co-administration of bedaquiline and clofazimine; five of them also received moxifloxacin. In particular, three (15%) patients had a transient and asymptomatic QTcF interval prolongation to >500 ms after 1 month of exposure, which subsequently reverted after only 1 week.

A second study by Guglielmetti *et al.* [35] reports on the prolonged administration of bedaquiline (*i.e.* >24 weeks). The French cohort included 73% of 45 patients who were administered bedaquiline for a median duration of 361 days. No correlations were seen between QTc prolongation and bedaquiline exposure. Only 6.7% interrupted their treatment due to QTc prolongation but no significant differences in safety and tolerability were observed between those belonging to the standard versus the prolonged duration arm. These findings are consistent with a previous case report described by Lewis *et al.* [36].

Information about cardiac safety of bedaquiline in association with clofazimine or fluoroquinolones is still scanty [37]. The Guglielmetti *et al.* [35] study suggests that co-administration of clofazimine is not associated with QTc prolongation, while the administration of both high-dose moxifloxacin and methadone was associated with QTcF values >500 ms.

TABLE 1 Clinical studies recently published on bedaquiline

First author [reference]	Year	Type of study	Patients exposed to bedaquiline	Efficacy findings	Tolerability findings	QTc effect	Notes
Guglielmetti [33]	2016	Retrospective study comparing microbiological outcome in bedaquiline-treated and fluoroquinolone-treated patients	25	No statistical differences in terms of culture conversion rates after 6 months between bedaquiline- and fluoroquinolone-treated patients (93% *versus* 96%)	No information reported	No information reported	Part of the cohort has been previously reported [82]
Udwadia [34]	2016	Prospective cohort study (compassionate programme)	20	Culture conversion rate was 64.7% after 6 months	No major adverse events	The QTcF intervals increased by a mean of 49 ms; a subset (5/20) of those exposed to bedaquiline and clofazimine also received moxifloxacin	
Guglielmetti [35]	2016	Retrospective cohort study	45	80% showed favourable outcome	Severe and serious adverse events were respectively observed in 60% and 18% of patients; no significant differences in outcomes or adverse events rates were observed between patients receiving standard and prolonged bedaquiline treatment	QTcF >500 ms values were recorded in 11% of patients, but neither arrhythmias nor symptomatic cardiac side effects occurred: bedaquiline was discontinued in 3 patients following QTcF prolongation	73% received prolonged treatment (>190 days), and 3 deaths occurred: 2 unexplained; 1 totally unrelated to the treatment
Lewis [36]	2016	Case report	1	Sputum and culture conversion after 4 weeks of bedaquiline-based treatment	No specific adverse events attributable to bedaquiline	QTc peaked after 10 weeks, after introduction of clofazimine; decreased after a few weeks from peak and after azithromycin discontinuation.	
Skrahina [37]	2016	Prospective cohort study (ongoing, preliminary data)	197	Culture conversion at 6 months was 94%, and 73.1%, 70.5%, and 62.2% in MDR-TB, pre-XDR-TB, and XDR-TB patients, respectively	Mild, moderate and reversible adverse events: hyperuricaemia, nausea, vomiting, abdominal pain, low platelet count and hepatic function abnormalities	41% experienced cardiac disorders (*e.g.* abnormal electrocardiogram and arrhythmia)	2 deaths occurred; one of them was considered related to MDR-TB treatment, not specifically to bedaquiline

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

New information on drug-drug interactions (DDIs) with antiretrovirals (ARVs) like lopinavir/ritonavir (LPV/r) and nevirapine (NVP) can be retrieved from pharmacokinetic (PK) studies [38, 39]. The PK profile of bedaquiline is characterised by extensive tissue distribution and an extremely long terminal half-life, exceeding 5 months [40]. Bedaquiline primarily undergoes N-demethylation catalysed by the cytochrome P450 (CYP) 3A4 enzyme, forming a three- to six-fold less active metabolite called M2 [41]. This CYP P450-mediated metabolism opens the issue of DDIs with ARVs [39]. Brill *et al.* [39] observed that bedaquiline clearance was reduced by NVP to 82% and M2 clearance increased to 119% of their original values, underpinning no clinically significant interactions. Conversely, LPV/r significantly reduced both bedaquiline and M2 clearance, increasing their concentrations. It is unlikely that NVP has a significant effect on bedaquiline and M2 clearance in patients with HIV/TB co-infection. Uncertainty remains on the clinical relevance of LPV/r-induced increased bedaquiline and M2 exposure.

On this basis, two potential pharmacological dynamics can be predicted following the increased bedaquiline concentration: 1) increased exposure may have a beneficial effect in terms of sputum-culture conversion [42]; 2) an increase of bedaquiline and, especially, of M2 concentrations could be associated with QTcF prolongation; thus, from a safety perspective, it would be advisable to adjust the bedaquiline dosage for those on concomitant LPV/r therapy until more data are available [39].

Interesting updates are now available from the introduction of bedaquiline-containing regimens at a programme level in selected countries and its scale up [43]. A recent report from South Africa highlighted success in implementing bedaquiline-based MDR-TB treatment in an outpatient setting [43]. In 2012, South Africa introduced an expanded access programme for bedaquiline, achieving promising preliminary outcomes [44]. In 2014, the South African Medicines Control Council approved and registered bedaquiline. Thus, bedaquiline use in South Africa has constantly increased (about 1100 patients started it in 2015) [45]. The majority required hospitalisation for safety concerns, although community-based MDR-TB services have been successfully launched in Khayelitsha [43, 46].

Nontubercular mycobacteriosis

In this issue of the ERJ, Vesenbeckh *et al.* [47] report on bedaquiline activity against *Mycobacterium intracellulare* and *Mycobacterium avium* strains. The authors evaluated minimum inhibitory concentrations (MICs) for 11 clinical strains of *M. intracellulare* and nine of *M. avium*, isolated from patients with pulmonary disease. The strains exhibited very low bedaquiline MIC (*M. intracellulare*: 0.06 $\mu g \cdot mL^{-1}$; *M. avium*: between 0.06 $\mu g \cdot mL^{-1}$ and 0.12 $\mu g \cdot mL^{-1}$), slightly higher than those known for TB, but comparable to those reported by other authors for the same mycobacteria [48]. Disease caused by *M. intracellulare* and *M. avium* strains, known also as *M. avium-intracellulare* complex (MAC), is a growing challenge with difficulties in identification, drug susceptibility testing (DST) execution, treatment regimen identification and length of treatment (usually >12 months) [49, 50].

Indeed, bedaquiline could become an effective candidate in the second-line treatment of mycobacterial disease caused by MAC. There are already reports about its successful use with MAC pulmonary disease [50]. In addition, other authors have recently reported very low MICs for bedaquiline on 103 respiratory MAC isolates, including MDR ones [51]. The study showed that approximately 90% of isolates had bedaquiline MICs of $\leqslant 0.008$ $\mu g \cdot mL^{-1}$ and 102 out of 103 isolates had MICs of $\leqslant 0.015$ $\mu g \cdot mL^{-1}$.

Alexander *et al.* [52] reported an interesting experience of off-label use of bedaquiline as salvage therapy for MAC lung disease, wherein seven of 13 patients had an initial microbiological response, but they later relapsed. Whole genome comparison of pre-treatment and relapse isolates of *M. intracellulare* uncovered mutations in a previously uncharacterised locus, mmpT5. There could be similarities between mmpT5 and the mmpR5 locus, which is associated with low-level bedaquiline resistance in TB.

Open issues on bedaquiline

Paediatric use of bedaquiline

Childhood TB, and specifically MDR-TB, remains a significant underestimated public health issue, particularly in low- and middle-income countries, where the TB burden is relevant [1, 7, 53, 54].

Unfortunately, one of the key aspects of childhood TB management, *i.e.* microbiological diagnosis (only a minority of TB cases in children is bacteriologically confirmed) affects one of the most important tools employed in designing an effective MDR-TB regimen, *i.e.* isolation of *Mycobacterium tuberculosis* with execution of DST. Thus, empirical administration of second- and third-line anti-TB drugs mainly relies on medical history related to previous contacts [54–57].

After a period of neglect, a phase-2 Janssen-sponsored clinical trial aiming to study PK in children (NCT02354014) is currently recruiting in Russia and South Africa [58]. In addition, a National Institute of Allergy and Infectious Diseases (NIAID)-sponsored phase 2 clinical trial (NCT02906007) aiming to

evaluate PK safety and tolerability in a paediatric population of USA and South Africa was planned to start in December 2016 [59].

Co-administration of bedaquiline and delamanid

Combined use of delamanid and bedaquiline is not currently recommended by WHO [20, 60, 61], although criteria were proposed to identify patients and settings where such a combination might be administered [20]. Only a couple of cases have received 6 months of combined treatment so far [62–64]. Safety and efficacy observed in these cases cannot allow for definitive conclusions. Further evidence is needed to estimate potential adverse events. In this regard, an NIAID-sponsored phase 2 clinical study has been started in Peru and South Africa (NCT02583048) [65].

In addition, the combination of delamanid and bedaquiline and, eventually, of other QT interval-prolonging drugs (*e.g.* fluoroquinolones, clofazimine) is prone to adverse events and potentially dangerous QTc prolongations [66]. The recommendation to regularly perform ECG during treatment with such drugs to monitor QT interval is not only "forma" but also clinically relevant.

Given these arguments, only specialised centres should eventually manage these difficult-to-treat cases, according to the criteria proposed [20], possibly under the guidance of a panel of experts such as the TB Consilium [62, 67]. In paediatric settings, no published evidence is still available, although clinically-based recommendations have been recently published [57] and a recent study by *Medecines Sans Frontieres* (MSF) reports on the actual needs to increase the availability of such new drugs [68]. Interestingly, a preliminary report from MSF projects recently presented in Liverpool on 24 cases [69] seems to be encouraging.

Resistance testing

It is now well known that resistance to bedaquiline might occur [70–72]. A mutant atpE gene seems to be responsible for such resistance in many cases [73]. In a large study by Pym *et al.* [70] published last year, 12 patients had a post-baseline greater than four-fold increase in bedaquiline MIC; all cases were associated with mutations in Rv0678, a transcriptional repressor of the MmpS5-MmpL5 efflux pump. Recently, resistance-associated variants (RAVs) in Rv0678 have been identified to be responsible for low-level resistance to bedaquiline and clofazimine [74–76]. Usually, they determine an increase in increased MICs of bedaquiline (two- to eight-fold) and clofazimine (two- to four-fold).

A 2016 study reported such RAVs in more than 300 MDR-TB strains. Rv0678 RAVs were identified in 23/347 (6.3%) of MDR-TB baseline isolates from patients enrolled in bedaquiline trials [77]. Interestingly, the occurrence of any RAV was not associated with prior use of bedaquiline or clofazimine, and did not lead to an increase in bedaquiline MIC above the provisional breakpoint (0.24 $mg{\cdot}L^{-1}$). Another study, published in this issue of the ERJ, reports on bedaquiline-resistance detection in MDR/XDR-TB strains [78]. In a 2-year period (2014–2015), 209 MDR/XDR-TB strains were tested for bedaquiline susceptibility; among these, four unrelated strains (2%) had elevated bedaquiline MICs (between 0.25 and 0.5 $mg{\cdot}L^{-1}$). As two patients harbouring a resistant strain had never been exposed to bedaquiline or clofazimine, authors proposed three possible explanations: 1) bedaquiline-resistance was selected by clofazimine treatment; 2) other compounds could promote bedaquiline resistance through *rv0678* mutations, since the recognised mechanism of resistance affects an efflux pump; 3) spontaneous RAVs occurred (as discussed above). The other two patients had previously been treated with bedaquiline, and the simple explanation would be that background regimen failed to prevent the selection of drug resistance.

The unfortunate reality is that, currently, an agreed-upon protocol to test bedaquiline susceptibility has not yet been developed [79, 80]. Nevertheless, a multi-laboratory, multi-country study to determine bedaquiline MIC quality control ranges for phenotypic DST has been recently conducted [81]. Results in terms of methodologies and quality control ranges have been submitted to the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to inform future research and provide guidance for routine clinical bedaquiline phenotypic DST.

Conclusions

Bedaquiline is an interesting drug for the treatment of MDR- and XDR-TB. Further evidence has been published on its tolerability, and its safety profile seems better today than initially expected.

Bedaquiline is not the single solution to all problems related to MDR-TB management. The great expectations on bedaquiline to improve MDR/XDR-TB patients' outcomes are tempered by concerns that mismanagement might occur when introducing it at the programmatic level.

Nevertheless, better results will be obtained if programmes could ensure adequate treatment and follow-up in specialised centres with comprehensive patient support, appropriate management of adverse events, free-of-charge treatment, and social support for vulnerable populations, availability of quality DST in reference

laboratories, tailored treatment regimens and lung surgery when indicated [35]. Prolonged treatment with bedaquiline could further improve treatment outcomes, although more evidence is needed [35, 36].

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