



# Bedaquiline for the treatment of multidrug-resistant tuberculosis: another missed opportunity?

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**Scale-up of introduction of bedaquiline, as part of optimised treatment regimens, is supported by growing evidence** <http://ow.ly/JCEV30aPLmq>

**Cite this article as:** Guglielmetti L. Bedaquiline for the treatment of multidrug-resistant tuberculosis: another missed opportunity? *Eur Respir J* 2017; 49: 1700738 [<https://doi.org/10.1183/13993003.00738-2017>].

5 years after its first approval by a stringent regulatory authority, the role of bedaquiline in the treatment of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) is well established, and acknowledged by existing guidance. However, in many regards, the global introduction of bedaquiline can hardly be considered as a success.

Bedaquiline, an innovative compound belonging to the diarylquinoline family, was developed in 2005 [1], and approved by the Food and Drug Administration and the European Medicines Agency in 2012 and 2013, respectively. The results of two phase IIb clinical trials have shown promising results when adding bedaquiline to an optimised background MDR-TB regimen [2–5], and raised new hopes in a field, like drug-resistant TB treatment, which had not seen any relevant innovation for decades. However, except for a few countries leading the way in the early programmatic introduction of bedaquiline [6], the global roll-out of this drug has been inadequate. According to a report by the Drug-Resistant TB Scale-up Treatment Action Team (DR-TB STAT), no more than 8195 patients globally were reported to have received treatment with bedaquiline before March 2017, with the large majority of them (59.6%) being treated in only one country, South Africa [7]. The disproportion between these numbers and the need for bedaquiline is striking: according to estimates provided by a multicentre study that included MDR-TB patients from the World Health Organization's (WHO) Europe and Africa regions, approximately one-third of patients would be eligible for treatment with bedaquiline based on drug-resistance criteria [8]. Moreover, the proportion of eligible patients exceeds two-thirds of all cases if we include those with baseline risk factors for poor outcome, as suggested by the recently updated WHO recommendations on the use of bedaquiline [9].

Unfortunately, the slow pace of the introduction of bedaquiline has not prevented the appearance of strains with resistance to this drug [10–12]. Although drug resistance has inevitably followed the

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Received: April 10 2017 | Accepted after revision: April 10 2017

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introduction of new antibiotics in the history of antimicrobial chemotherapy, some of the practices that are currently established in the use of bedaquiline may arguably increase the risk of resistance selection [13]. In most settings, bedaquiline is used for 24 weeks as a component of conventional regimens, which usually last 20–24 months. The standardised duration of bedaquiline treatment is recommended by the manufacturer according to the evidence provided by clinical trials where bedaquiline was given for 24 weeks. This recommendation does not take into account the specific needs of individual MDR-TB patients. The interruption of bedaquiline treatment may lead to the administration of unacceptably weak regimens in cases where no therapeutic alternatives are available. A recent study confirms these concerns: in the study, almost 20% of 53 MDR-TB patients who had achieved sputum culture conversion with bedaquiline-containing regimens experienced reversion to positive cultures after interrupting bedaquiline treatment at 24 weeks [14]. In addition, current recommendations warn against the concomitant use of the new drugs, bedaquiline and delamanid, on the grounds of a lack of evidence and the potential for a synergic increase in QT interval prolongation. Even if based on understandable safety concerns, an excess of prudence in this case may lead to prioritising the prevention of the virtual risk of cardiac toxicity over the well-documented risk of death associated with drug-resistant TB. Indeed, the association of bedaquiline and delamanid may represent the only chance of an effective treatment for XDR-TB cases with advanced resistance patterns or intolerance to multiple drugs. The sequential use of the new drugs, after a recommended wash-out period of 6 months when switching from bedaquiline to delamanid, contradicts the principles of anti-TB treatment and may increase the risk of acquisition of drug resistance, as exemplified by a case report in which resistance to bedaquiline and delamanid was acquired sequentially during treatment [12, 15, 16].

The shortcomings in global access to bedaquiline are reflected by the paucity of available evidence [17, 18]. Only a few treatment cohorts including at least 10 patients have been published to date [19–23], and only one reporting treatment outcomes [24]. Extended treatment duration with bedaquiline has so far been described in one small cohort and in a case report [24, 25], and only two case reports of concurrent treatment with bedaquiline and delamanid have been published [26, 27].

These research gaps emphasise the importance of the study by BORISOV *et al.* [28] presented in this issue of the *European Respiratory Journal*, which reports the results of the first large multicentre cohort of patients receiving bedaquiline-containing treatment. This retrospective cohort study involved 25 centres from 15 different countries, including settings with both high and low TB burden. Consecutive, culture-confirmed MDR-TB patients treated outside clinical trials with a regimen including bedaquiline in the period between 2008 and 2016 were included in the study, regardless of the timing of bedaquiline introduction. Treatment efficacy was assessed through sputum culture conversion rates and, for patients who ended treatment, the outcomes of the treatment. Treatment safety data was collected, including QT interval follow-up when available, although no standardised protocol to grade severity and seriousness of the adverse events, nor their causality link with bedaquiline, was implemented. Overall, 428 MDR-TB patients were included, mostly from South Africa (44%) and the Russian Federation (28%). The cohort includes high rates of XDR-TB (46%) and previously treated (78%) cases, and a total prevalence of HIV infection of 22% among those tested. Treatment regimens included, in more than half of cases, re-purposed drugs like linezolid and clofazimine. Sputum culture conversion rates were 57% and 81% at 2 and 3 months after anti-TB treatment commenced, respectively. Remarkably, 77% of the 130 patients in the 2008–2014 cohort, which included patients with  $\geq 2$  years of follow-up, achieved favourable treatment outcomes. These figures appear to be consistent with the outcomes of patients starting treatment after 2014, although the results of these recent cohorts are preliminary and should be interpreted carefully. As expected with MDR-TB regimens, a high rate of adverse events occurred during treatment. Treatment with bedaquiline was interrupted in 12% of patients, and discontinued permanently in 6%: the reasons for discontinuation were not reported. QT interval corrected according to the Fridericia formula (QTcF) values of  $>500$  ms were recorded in 24 out of 247 (9.7%) patients with available data. Among the patients who died and had available QT follow-up information, no one experienced QT prolongation, with the exception of one patient who already had  $>500$  ms QTcF at baseline. One patient died after developing a severe ventricular arrhythmia, although his QTcF never exceeded 500 ms.

Overall, this collaborative study provides us with a wealth of evidence on the use of bedaquiline. First of all, the efficacy results are remarkable. The rate of favourable outcomes in the cohort who commenced treatment before 2014 is in line with the upper boundary of the confidence interval of the meta-analysis included in the latest WHO recommendations [9], and is much higher than those reported in systematic reviews of MDR/XDR-TB patients treated without new and repurposed drugs [8, 29, 30]. Early culture conversion rates are also high, although the inclusion of patients starting bedaquiline at different time-points during treatment makes it difficult to single out the role of bedaquiline. Although prone to the shortcomings of retrospective, non-standardised data collection, safety results are reassuring. This is in line

with other published reports [19, 22–24] and with the conclusions of the recently revised WHO recommendations, which downgraded the anticipated undesirable effects of bedaquiline from “large” to “moderate” [9].

In this framework, the study by BORISOV *et al.* [28] represents a source of information that should not be overlooked. The authors’ encouraging results bring additional evidence to support a systematic introduction of bedaquiline for patients who need it. At the same time, they highlight the urgent need for well-documented prospective observational cohorts of patients receiving bedaquiline in the years before results from phase III clinical trials will become available. The timely roll-out of bedaquiline will require, in parallel, increased attention to prevent drug resistance, including optimal, individualised patient management. The use of prolonged bedaquiline treatment and the combination of bedaquiline and delamanid are therapeutic options that should be considered whenever indicated. Criteria have already been proposed to guide the selection of such patients [24, 31]. This is the time to scale-up and improve our efforts to avoid bedaquiline being remembered as another missed opportunity in the history of TB control.

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