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Is bedaquiline as effective as fluoroquinolones in the treatment of multidrug-resistant tuberculosis?

To the Editor:

Bedaquiline (Bdq) is approved for the treatment of multidrug-resistant (MDR) tuberculosis (TB). In a phase IIb trial, Bdq allowed a significant reduction in time to culture conversion and improved outcome in MDR-TB patients [1, 2]. Preliminary reports of Bdq compassionate use have shown promising results [3–5]. However, in an early bactericidal activity (EBA) study, the association of moxifloxacin (Mfx) with PA-824 and pyrazinamide showed better activity than Bdq-based associations [6]. In addition, resistance to fluoroquinolones (Fq) has been associated with poorer outcome in MDR-TB before Bdq use [7]. These data reinforce the pivotal role of Fq. Comparing Bdq to Fq in interventional studies is challenging. Indeed, the paucity of drugs available for MDR-TB treatment, and the need for combination therapy, often impose the need to use all available drugs.

In an interim analysis of a Bdq-treated MDR-TB cohort, we showed that culture conversion reached 96% with 6-month Bdq-containing treatment regimens [8]. Following these encouraging results, we sought to compare the microbiological efficacy of Bdq- and Fq-containing regimens.

A retrospective study comparing microbiological outcome in Bdq-treated and Fq-treated patients was designed using the 2006–2014 cohort of MDR-TB patients hospitalised at Bligny's Sanatorium (Briis-sous-Forges), a French referral TB centre. The first group included patients treated for ⩾30 days with Bdq, who either had not received any Fq or had received Fq but harboured *Mycobacterium tuberculosis* isolates with high-level phenotypical Fq resistance. The second group comprised patients treated for ⩾30 days with any Fq but without Bdq, with isolates susceptible to ofloxacin (Ofx) and Mfx. All patients received any second-line injectable drug and linezolid for ⩾30 days, and had positive sputum cultures at treatment start.

All regimens were individually tailored according to the drug susceptibility test (DST) results and were started at the hospital where the diagnosis was made or at the Bligny Sanatorium. All drugs were administered under direct observation and according to international guidelines [9]. Sputum cultures were repeated every 2 weeks up to culture conversion, and monthly thereafter. Time to culture conversion was measured from treatment start to the first of two consecutive negative culture results.

The DST was performed at the French National Reference Center for Mycobacteria (Paris) on Löwenstein–Jensen medium by the critical proportion method [10]. Resistance to Ofx was defined as mycobacterial growth at a concentration ⩾2 $mg{\cdot}L^{-1}$. High-level Fq resistance was defined as mycobacterial growth at a concentration ⩾2 $mg{\cdot}L^{-1}$ of Mfx.

Statistical analysis was performed with STATA (StataCorp, College Station, TX, USA). Categorical variables were compared using Chi-squared or Fisher's exact test, and continuous variables by the Wilcoxon–Mann–Whitney test. Kaplan–Meier curves for culture conversion were estimated. The Mantel–Cox test was used to compare time to culture conversion between the two groups. A Cox proportional hazards model was used to estimate the association between explanatory variables and time to culture conversion. Variables associated in univariate analysis ($p<0.20$) were considered for backward multivariable analysis. p-values <0.05 were considered as significant.

Bdq was provided under the national compassionate use programme, and patients received information regarding this programme and the safety profile of all drugs. The Institutional Review Board of Bligny's Hospital granted ethical approval.

The cohort included 119 MDR-TB patients with a positive sputum culture at the beginning of anti-TB treatment. Among them, 86 received both linezolid and any second-line injectable drug for ⩾30 days, and 25 Bdq-treated and 42 Fq-treated patients were finally included. The median age of the 67 patients was 33 years (interquartile range (IQR) 27–40 years). A majority was male (n=50; 75%) and foreign-born (n=60; 90%). 35 (52%) patients harboured isolates susceptible to any Fq and second-line injectable drug, 16 (24%) had isolates with additional resistance to only one of these two drug classes and 16 (24%) to

both. Among the 25 Bdq-treated patients, 17 (68%) never received Fq and eight (32%) received levofloxacin (Lfx), Mfx or both successively. Among the 42 Fq-treated patients, 36 (86%) received Mfx, four Lfx and two both successively. Compared with Fq-treated patients, Bdq-treated patients were more likely to be male (96% *versus* 62%; p=0.001), born in Eastern Europe (84% *versus* 33%; p<0.001), to have received prior TB treatment (92% *versus* 55%; p=0.002) and to have bilateral pulmonary involvement (100% *versus* 76%; p=0.010). There was no difference regarding the presence of lung cavities and sputum smear status at treatment start. Three patients were HIV positive, all in the Fq-treated group. The median number of drugs to which isolates were susceptible was five in the Bdq group and eight in the Fq group (p<0.001). Bdq-treated patients were less likely to receive ethambutol (28% *versus* 59%; p=0.022) and ethionamide (20% *versus* 48%; p=0.036) but more likely to receive clofazimine (32% *versus* 5%; p=0.004) and carbapenem-clavulanate (48% *versus* 2%; p<0.001). No difference was found in the proportion of patients treated with pyrazinamide, streptomycin, cycloserine and para-aminosalicylic acid.

The 3-month culture conversion rate was higher in Fq-treated than in Bdq-treated patients (74% *versus* 44%; p=0.02), while no statistical difference was found at 6 months (93% *versus* 96%, respectively). The median (IQR) time to culture conversion was shorter for Fq-treated than for Bdq-treated patients (60 (35–89) days *versus* 98 (70–124) days; p=0.005) (figure 1).

In a multivariate proportional hazard model, variables remaining associated with faster time to culture conversion were absence of lung cavities (hazard ratio (HR) 6.60, 95% CI 3.21–13.56; p<0.001), negative sputum smear at treatment start (HR 4.73, 95% CI 1.01–22.08; p=0.048) and female sex (HR 3.22, 95% CI 1.65–6.30; p=0.001). Other variables, including the treatment group, were not significantly associated with time to culture conversion in the multivariate model.

Our study showed no difference in culture conversion rate between Bdq-treated and Fq-treated patients at 6 months. This is promising for Bdq-treated patients, as the 6-month end-point has been linked to successful outcome [11]. Moreover, these results were observed while the characteristics of Bdq-treated patients (bilateral pulmonary involvement, number of drugs for which susceptibility was demonstrated) suggest that they are more difficult to treat than the others.

Nevertheless, time to culture conversion was slower in the Bdq-treated than in the Fq-treated group. This is consistent with previous EBA studies [6, 12]. However, the difference may be due to companion drugs [13]. Indeed, Bdq-treated patients were less likely to receive ethambutol and ethionamide. Interestingly, in the multivariate analysis, Fq-containing regimens were not associated with faster time to culture conversion, while TB characteristics (absence of lung cavitations and smear-negative TB) were the most determinant factors.

Female sex was linked to faster time to culture conversion, but all but one female patient were in the Fq group. Nevertheless, male sex was reported as an independent risk factor for mortality in MDR-TB [14].

In the Bdq-treated group, the achievement of culture conversion closer to the 6-month end-point may suggest continuing Bdq after 24 weeks of treatment [9] for late converters, to prevent culture reversion.

Our study is limited by its observational nature. Moreover, the fact that one third of the Bdq patients with Mfx-resistant isolates received Fq during the treatment course may have affected the results. However, Mfx resistance is almost constantly associated with high-level resistance to other Fq [15]. Hence, it is unlikely that Fq treatment had an impact on culture conversion in the Mfx-resistant Bdq-treated group.

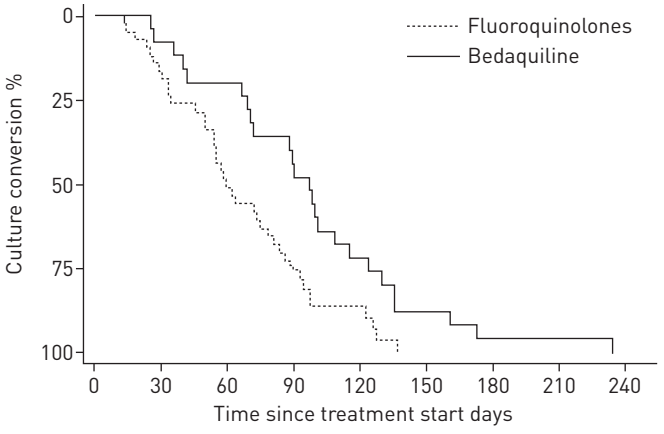

FIGURE 1 Kaplan–Meier curves of sputum time to culture conversion in the bedaquiline- and fluoroquinolone-treated patients.

Our study suggests that the 6-month culture conversion rate is similar with Bdq- and Fq-containing regimens. The slower time to culture conversion in the Bdq-treated group could be explained by the patient case mix and differences in the background regimen. Further studies are needed to relate the difference in time to culture conversion with treatment outcome.

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Bedaquiline and fluoroquinolone treatments give similar culture conversion rates at 6 months in MDR-TB patients http://ow.ly/oqVY300mJCy

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