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

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Is bedaquiline as effective as fluoroquinolones in the treatment of MDR tuberculosis: a retrospective analysis of a French cohort

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Bedaquiline (Bdq) is approved for the treatment of multidrug-resistant tuberculosis (MDR-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 [7]. In addition, resistance to Fq has been associated with poorer outcome in MDR-TB before Bdq use [8]. These data reinforce the pivotal role of fluoroquinolones (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 using 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 [9]. 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 hospitalized at Bligny's Sanatorium, a French referral TB centre. The first group includes patients treated for ≥30 days with Bdq, and either not having received any Fq or having received Fq but harbouring *Mycobacterium tuberculosis* isolates with high-level phenotypical Fq resistance. The second group comprises 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 sanatorium. All drugs

were administered under direct observation and according to international guidelines [10]. Sputum cultures were repeated every two 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.

DST was performed at the National Reference Centre for Mycobacteria on Löwenstein-Jensen medium by the critical proportion method [11]. Resistance to Ofx was defined as mycobacterial growth at a concentration ≥2 mg/l. High-level Fq resistance was defined as mycobacterial growth at a concentration ≥2 mg/l of Mfx.

Statistical analysis was performed with STATA (StataCorp, Texas, USA). Categorical variables were compared by using Chi-square 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 program, and patients received information regarding this program 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-tuberculosis 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). A majority (n=50; 75%) was male and foreign-born (n= 60; 90%). Thirty-five patients

(52%) harboured isolates susceptible to any Fq and second-line injectable drug, 16 (24%) had isolates with additional resistance to only one of this two drug classes and 16 (24%) to both. Among the 25 Bdq-treated patients, 17 (68%) never received Fq and 8 (32%) received levofloxacin (Lfx), Mfx or both successively. Among the 42 Fq-treated patients, 36 (86%) received Mfx, 4 Lfx, and 2 both successively. Compared to 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), having 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 5 in the Bdq-group and 8 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 (74%) than in Bdq-treated patients (44%; p=0.02), while no statistical difference was found at 6 months (93% *versus* 96%, respectively). The median time-to-culture conversion was shorter for Fq-treated (60 days, IQR 35-89) than for Bdq-treated patients (98 days, IQR 70-124; p=0.005) (Figure).

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% Confidence Interval (CI) 3.21-13.56, p<0.001], negative sputum smear at treatment start (HR: 4.73, 1.01-22.08, p=0.048), and female sex (HR: 3.22, 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 shows 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 [12]. Moreover, these results are observed while the characteristics of Bdq-treated patients (bilateral pulmonary involvement, number of drug 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, 7]. However, the difference may be due to companion drugs [13]. Indeed, Bdq-treated patients were less likely to receive ethambutol and ethionamide. Of interest, 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 endpoint may suggest continuing Bdq after 24 weeks of treatment [10] 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 impacted the results. However, Mfx resistance is almost constantly associated with high-level resistance to other Fq [15]. Hence, it is unlikely that Fq treatment impacted culture conversion in the Mfx-resistant Bdq-treated group.

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 patients' case-mix and difference in the background regimen. Further studies are needed to relate the difference in time-to-culture conversion to treatment outcome.

Figure

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

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