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Should we worry for bedaquiline exposure in the treatment of MDR- and XDR-TB?

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Recently, the World Health Organization (WHO) released the updated guideline on the treatment for multi-drug resistant tuberculosis (MDR-TB) treatment regimens based on new experimental and observational evidence[1]. In this new guidance the most important drugs are the late-generation fluoroquinolones (i.e., levofloxacin and moxifloxacin), linezolid, and bedaquiline. Despite the new guidance MDR- and extensively drug resistant (XDR) TB treatment is challenging due to the risk of drug-related adverse events (AE) and drug-drug interactions (DDI). Precision medicine-based approach to minimize the risk of resistance emergence and amplification and to provide patients with the highest standard of care has been recommended[2]. Variable exposure to second-line anti-TB drugs, which has been proved in several studies, can cause either AEs or lack of response because of too high or low concentrations, respectively. Therapeutic drug monitoring (TDM) has, therefore, been recommended to provide information on the individual drug concentration[2, 3]. In the past decade TDM has been frequently prescribed in well-resourced settings with promising results; on this basis, the American Thoracic Society TB guidelines have endorsed TDM in specific situations[4, 5]. The strongest evidence on TDM in the management of M/XDR-TB is related to fluoroquinolones and linezolid[6, 7]. In vitro studies showed a clear relationship between drug exposure, susceptibility of *M. tuberculosis*, and reduction in bacterial load, and cure. Observational research proved that slow therapeutic response and acquired drug resistance are likely associated with poor drug exposure. In the recently update WHO guideline on MDR-TB treatment TDM has been recommended for fluoroquinolones, linezolid and aminoglycosides, especially when “the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure”[1]. Unfortunately, randomized controlled studies on TDM have not been planned until now.

Bedaquiline-containing regimens showed their efficacy and effectiveness in experimental and observational studies. However, factors interfering with its pharmacokinetics may affect its concentrations. In particular, bedaquiline absorption is influenced by food and DDI, being metabolized by CYP450 enzymes. A post-hoc analysis of the pharmacokinetic data collected in trials
setup for regulatory approval showed that higher bedaquiline exposure had a beneficial effect on time to sputum culture conversion. In a subsequent covariate analysis weight, albumin, age, and race were associated with drug exposure[8]. However, strict selection criteria of the regulatory studies might have biased those results. It is key to prove the same and/or other factors in the real-life world and their association with clinical and treatment outcomes, including the occurrence of AEs. If such a relationship would be present, this could prove the necessity of exploring the added value of TDM for bedaquiline.

The aim of the present study was to evaluate whether factors associated with altered pharmacokinetics of bedaquiline are present in a large multi-center cohort of M/XDR-TB patients treated under different real-life conditions.

We performed an observational retrospective study. For patient recruitment, ethical clearance, TB case definition, treatment design, and study period we refer to the original study [9]. Bedaquiline was prescribed at the licensed dose of 400 mg once a day for 14 days, followed by 200 mg three times a week for 22 weeks. A standardized e-form was developed and used to collect epidemiological, clinical, and microbiological data from medical records. Several factors related to lower bedaquiline exposure were included in the case-report form: increased bodyweight, co-prescription of a strong inductor of CYP3A4; prior use of rifampicin for >10 days and stopped <2 weeks before the administration of bedaquiline; uncontrolled HIV infection, diabetes mellitus and gastrointestinal complaints. Moreover, factors related to higher bedaquiline exposure were recorded: increasing age, strong inhibitor of CYP3A4.

A total of 428 patients was available for the analysis. For a detailed description of demographics, epidemiological and clinical characteristics (including AEs) we refer to the original study[9]. Table 1 summarizes the frequency of risk factors associated with either low or high exposure.

Although administration with food is recommended, it was observed that 125 patients (30.3%) received bedaquiline in fasted condition. Administration without food reduces drug exposure of ~50% [10] and may, therefore, have resulted in suboptimal exposure. In addition, bedaquiline co-
administered with strong CYP 3A4 inducers occurred in 81 (27.2%) patients. Data on the impact of the different drug-drug interaction is scarce but it was shown that rifampicin and rifapentine reduced bedaquiline drug exposure with approximately ~40-80% [11]. Moreover, simulation studies showed that evafirenz reduced drug exposure of 50% [12]. Based on the results of these 3 strong inducers of CYP3A4 it can be assumed that any other strong inducer would exert a similar effect on bedaquiline exposure. Other factors that may have impacted bedaquiline exposure were also observed. Higher body weight, low albumin concentration, uncontrolled HIV infection, and gastrointestinal problems may have a detrimental effect on drug exposure but are more difficult to quantify. Even more challenging is to estimate the consequences of a combination of factors on drug exposure. Six cases, who received the drug without food but with a strong CYP 3A4 inducer, showed the following treatment outcomes: 4 were still on treatment, 1 was cured, and 1 was lost to follow-up. Our study was not the only study showing risk factors that could influence bedaquiline exposure.

In the study by Ndjeka et al. 200 patients received a bedaquiline containing treatment regimen for M/XDR-TB [13]. The cohort included 134 patients living with HIV. As part of their antiretroviral regimen 101 patients received nevirapine, a strong CYP 3A4 inductor and 34 patients received ritonavir, a strong inhibitor of 3A4, resulting in either reduced or increased bedaquiline exposure. A similar situation was observed in a cohort receiving bedaquiline in combination with delamanid as compassionate use [14]. In that study of 46 of the 84 patients were co-infected with HIV potentially receiving a strong CYP3A4 inductor or inhibitor.

Factors influencing bedaquiline drug exposure are frequently present and are not only proved by our large retrospective study but also by other studies [13, 14]. Although the impact is difficult to estimate because actual drug exposure measurements are lacking, prospective evaluation is needed to estimate the impact of drug influencing factors in a real-life setting. The nature of the design should be observational, and the study should be performed in an operational setting, as strong evidence from clinical trials to support therapeutic drug monitoring is lacking. Although it can be
speculative, it seems plausible that at least a subset of patients might benefit from the assessment of drug exposure.

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References


### Table 1. Risk factors for low and high bedaquiline drug exposure

<table>
<thead>
<tr>
<th>Factor</th>
<th>Median (IQR)</th>
<th>Number of subjects (%)</th>
<th>total subjects with data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“low”</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight &gt;80 kg</td>
<td>84 (82.3-92) kg</td>
<td>19 (5.3)</td>
<td>359</td>
</tr>
<tr>
<td>Albumin &lt;32 gr/L</td>
<td>28 (25-30) gr/L</td>
<td>76 (22.4)</td>
<td>340</td>
</tr>
<tr>
<td>Without food</td>
<td></td>
<td>125 (30.3)</td>
<td>413</td>
</tr>
<tr>
<td>Strong inducer of CYP3A4#</td>
<td></td>
<td>81 (27.2)</td>
<td>298</td>
</tr>
<tr>
<td>Prior use of RIF</td>
<td></td>
<td>9 (2.2)</td>
<td>403</td>
</tr>
<tr>
<td>Uncontrolled HIV (CD4 lymphocytes &lt;200 cells/mmc)</td>
<td>99 (44.5-159.5)</td>
<td>28 (31.5)</td>
<td>89</td>
</tr>
<tr>
<td>DM2</td>
<td></td>
<td>26 (6.3)</td>
<td>413</td>
</tr>
<tr>
<td>Gastrointestinal complaints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>87 (21.2)</td>
<td></td>
<td>411</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>56 (13.6)</td>
<td></td>
<td>412</td>
</tr>
<tr>
<td>Both</td>
<td>26 (6.3)</td>
<td></td>
<td>410</td>
</tr>
<tr>
<td><strong>“high”</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodyweight &lt;50 kg</td>
<td>43 (38.7-46)</td>
<td>114 (31.8)</td>
<td>359</td>
</tr>
<tr>
<td>Age &gt;70 yrs</td>
<td>78 (72-80)</td>
<td>5 (1.2)</td>
<td>428</td>
</tr>
<tr>
<td>Strong inhibitor of CYP3A4#</td>
<td></td>
<td>26 (8.7)</td>
<td>298</td>
</tr>
</tbody>
</table>