Commentary

Bedaquiline Phenotypic and Genotypic Susceptibility Testing, Work in Progress!

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Criteria to define phenotypic resistance to bedaquiline (BDQ) are not well determined and uncertainties around the genetic basis of resistance and cross resistance with clofazimine (CFZ) for this novel drug continue (Keller et al., 2015; Villelles et al., 2017; Xu et al., 2017). It is essential that susceptibility criteria for Mycobacterium tuberculosis (MTB) isolates towards new and repurposed drugs are established, given their increasing relevance in the new WHO treatment recommendations (Borisov et al., 2017; Falzon et al., 2017).

The study reported by Ismail and colleagues in EBioMedicine addresses this important topic (Ismail et al., 2018). The study was performed in the Republic of South Africa, a country with a high burden of drug resistant tuberculosis (TB) and a major prescriber of BDQ with approximately 7420 of the 12,194 courses dispensed worldwide (Country Updates (Internet), 2017). Interestingly, the Authors suggest the establishment of an intermediate category is supported by the fact that all 8 persistently positive patients had 6-month isolates with BDQ MIC above 0.125 mcg/ml.

Cross-resistance to BDQ and CFZ is a topic of great interest given the recent WHO recommendations for use of a short-course CFZ-containing regimen for MDR-TB6 and further evidence from the STREAM trial indicating that this regimen is effective. The data certainly suggests that CFZ resistance is a risk factor for BDQ resistance. However only 1/3 of CFZ intermediate/resistant strains are also BDQ resistant whilst all BDQ resistant isolates were susceptible to BDQ.

The important finding discussed by the authors was that BDQ-exposed isolates with Rv0678 mutations may have higher BDQ MICs than non-BDQ-exposed isolates with Rv0678 mutations. This raises important issues for baseline BDQ MIC testing and whether it is sufficiently sensitive to detect baseline Rv0678 mutations (that may be associated with greater likelihood of delayed or lack of clinical response). Importantly, the role of companion drugs might be crucial at preventing amplification of efflux-pump mutant subpopulations or even mutagenesis itself, as hypothesized by the authors.

The study has important limitations: there is no comparison with the proposed EUCAST reference in agar medium, the retrospective collection was limited to a single country and contained only few cases in the BDQ exposed group, and it was sponsored by Janssen and one of its employees contributed to the manuscript.

The study defines the isolates as susceptible to BDQ at MICs of ≤0.125 and ≤1 mcg/ml in 7H9 and MGIT, respectively. The EUCAST set ≤0.25 mcg/ml on 7H9 as concentration to define susceptibility and WHO has recently presented provisional critical concentrations of 0.25 and 1 mcg/ml in 7H11 and MGIT, respectively (Union Guadalajara 2017). Interestingly, the Authors suggest the “intermediate” category for isolates with MICs 0.25 and 2 mcg/ml on 7H9 and MGIT, respectively. The establishment of an intermediate category is supported by the fact that all 8 persistently positive patients had 6-month isolates with BDQ MIC of 0.25 mcg/ml (n = 3) or 0.5 mcg/ml (n = 5) on 7H9, whereas none of the patients who converted before 6 months had isolates with BDQ MIC above 0.125 mcg/ml.

Cross-resistance to BDQ and CFZ is a topic of great interest given the recent WHO recommendations for use of a short-course CFZ-containing regimen for MDR-TB and further evidence from the STREAM trial indicating that this regimen is effective. The data certainly suggests that CFZ resistance is a risk factor for BDQ resistance. However only 1/3 of CFZ intermediate/resistant strains are also BDQ resistant whilst all BDQ resistant strains were all found among susceptible isolates. All CFZ - susceptible isolates were susceptible to BDQ.

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and knowledge on BDQ genomic targets (including role of Rv0678) is still incomplete.

This study forms the basis for the implementation of phenotypic DST to determine BDQ resistance by using user-friendly microdilution methods and increases knowledge of the genetic determinants associated with resistance to this drug. Large-scale collection of quality-assured phenotypic and genotypic data as performed in this paper will allow moving faster towards the development of rapid and comprehensive approaches to test any new drugs coming on the market.

**Disclosure**

We declare no competing interests. All authors contributed to the manuscript.

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