Quantitation of Plasma Bedaquiline Concentrations in Indian MDR-TB Patients Using Liquid Chromatography-Tandem Mass Spectrometry

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Background: Bedaquiline (BDQ) is a diarylquinoline used for the treatment of multi drug resistant tuberculosis (MDR-TB). It has a large volume of distribution and a terminal half-life of 5.5 months. Its reported side effects are nausea, joint and chest pain, headache, arrhythmias and QTcF prolongation. A new regimen comprised of Bedaquiline, Pretomanid, Linezolid and Moxifloxacin (BPaLM) is now recommended in India as studies have shown it is a safer, more effective, and shorter treatment option than prior MDR-TB regimens. There are limited reports on the pharmacokinetics of BDQ in MDR-TB patients globally and very few from India, which warrant further studies. We performed a pilot study aimed to develop and validate a BDQ assay in plasma and apply it towards understanding the pharmacokinetics in Indian MDR-TB patients.

Methods: Plasma BDQ concentrations were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and the method was validated as per the bioanalytical method validation guidelines of the US Food and Drug Administration 2018. For the pharmacokinetic

study, blood samples were collected from adults and adolescents (≥ 15 years) patients with MDR-TB and on an ongoing BDQ regimen of 2 tablets of 100 mg dosed on alternate days of the week. Informed consent was taken from all patients and blood samples were collected at pre-dose (0 hour) and 1,2,4,6 and 8 hours post dose ingestion in K2-EDTA vacutainers. The samples were centrifuged and plasma was separated and preserved at -80°C until analysis. The area under the curve (AUC) from 0 to 8 hours was calculated using the trapezoidal rule.

Results: The calibration range was established between 0.0313 to 4.0 mg/L. The method met US FDA validation criteria and inter-lab comparison was performed with a reference laboratory. Intensive pharmacokinetic sampling was performed in 23 patients (52% females) and BDQ plasma concentrations were determined. The mean (SD) age and BMI of patients was 25.6 (7.6) years and 22.5 (5.7) kg/m^2 respectively. The median Cmax and time to peak plasma concentrations (Tmax) were found to be 1.59 mg/L and 6 hours, respectively. The median AUC for the 8 hour period was calculated as 9.79 mg·h/L spanning a range of 3.00 – 29.94 mg·h/L and the same was extrapolated to a 24-hour period with median AUC as 33.31 mg·h/l across a range of 11.09-81.98 mg·h/L.

Conclusion: A simple, selective, sensitive and robust LC-MS/MS method has been developed and validated for the determination of bedaquiline in human plasma. The method was successfully validated and applied to a pilot pharmacokinetic study. Our pharmacokinetic findings are similar to those reported in literature. The method can be used for routine therapeutic drug monitoring and future pharmacokinetic studies.