Drug exposure and susceptibility of second-line drugs correlate with treatment response in patients with multidrug-resistant tuberculosis: a multicentre prospective cohort study in China

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Drug exposure and susceptibility were proved to be associated with treatment responses during multidrug-resistant tuberculosis treatment, and identified thresholds may serve as targets for dose adjustment in future clinical studies to improve treatment efficacy https://bit.ly/3pZQbFU

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Abstract

Background Understanding the impact of drug exposure and susceptibility on treatment response of multidrug-resistant tuberculosis (MDR-TB) will help to optimise treatment. This study aimed to investigate the association between drug exposure, susceptibility and response to MDR-TB treatment.

Methods Drug exposure and susceptibility for second-line drugs were measured for patients with MDR-TB. Multivariate analysis was applied to investigate the impact of drug exposure and susceptibility on sputum culture conversion and treatment outcome. Probability of target attainment was evaluated. Random Forest and CART (Classification and Regression Tree) analysis was used to identify key predictors and their clinical targets among patients on World Health Organization-recommended regimens.

Results Drug exposure and corresponding susceptibility were available for 197 patients with MDR-TB. The probability of target attainment was highly variable, ranging from 0% for ethambutol to 97% for linezolid, while patients with fluoroquinolones above targets had a higher probability of 2-month culture conversion (56.3% *versus* 28.6%; adjusted OR 2.91, 95% CI 1.42–5.94) and favourable outcome (88.8% *versus* 68.8%; adjusted OR 2.89, 95% CI 1.16–7.17). Higher exposure values of fluoroquinolones, linezolid and pyrazinamide were associated with earlier sputum culture conversion. CART analysis selected moxifloxacin area under the drug concentration–time curve/minimum inhibitory concentration ($AUC_{0–24h}$/MIC) of 231 and linezolid $AUC_{0–24h}$/MIC of 287 as best predictors for 6-month culture conversion in patients receiving identical Group A-based regimens. These associations were confirmed in multivariate analysis.

Conclusions Our findings indicate that target attainment of TB drugs is associated with response to treatment. The CART-derived thresholds may serve as targets for early dose adjustment in a future randomised controlled study to improve MDR-TB treatment outcome.