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O0235 Predicting the outcomes of new short-course regimens for multidrug-resistant tuberculosis using intrahost and pharmacokinetic-pharmacodynamic modelling

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Background:

Short-course regimens for multi-drug resistant tuberculosis (MDR-TB) are urgently needed. Limited data suggest that bedaquiline (BDQ), when used in conjunction with other drugs, improves treatment outcomes and potentially shorten MDR-TB treatment duration to less than six months. Further assessment on the efficacy of short-course BDQ-containing regimens is required before recommendations can be made about its value in MDR-TB treatment. Mathematical models combining drug pharmacokinetics-pharmacodynamics (PK-PD) with the intrahost immune response can provide a platform to investigate different dosing strategies to identify highly effective regimens.

Materials/methods:

A mathematical model was developed to mimic the human immune response to TB. Major elements of the immune response to TB including macrophages, cytokines and lymphocytes were incorporated. This model was then combined with a PK-PD model to simulate various short-course BDQ-containing regimens, and estimate their anti-mycobacterial effects. These regimens consisted of an initial intensive phase with BDQ, moxifloxacin (MXF), clofazimine (CFZ), pyrazinamide (PZA), isoniazid (INH) and kanamycin (KNM), followed by a continuation phase with BDQ, MXF, CFZ and PZA. Various durations of treatment were investigated and a comparative analysis of their efficacy was undertaken in order to identify highly effective regimens.

Results:

We found that treatment duration for MDR-TB can be reduced to just 18 weeks while still maintaining a very high treatment success rate (100% for daily BDQ for two weeks during the intensive phase, or 95% when BDQ is given daily for one week during the intensive phase). The estimated time to bacterial clearance of these regimens ranges from 27 to 33 days. Achieving optimal exposure early, in the first four weeks of treatment, is critical for successful treatment. Intermittent dosing of MXF (three times weekly or weekly) does not compromise treatment efficacy.

Conclusions:

This study represents a novel approach to the global challenge of MDR-TB. Our study shows that MDR-TB treatment could potentially be further shortened to four months with BDQ. The findings provide the justification for empirical evaluation of short-course BDQ-containing regimens. If BDQ-containing regimens are found to improve outcomes then we anticipate clear cost-savings and a subsequent improvement in the efficiency of national TB programs.