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Commentary

Are the Present Doses of Anti Tubercular Drugs Adequate for Severe Disease?

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Tuberculosis (TB) continues to be a major global health issue, with the World Health Organization (WHO) reporting 9 million new TB cases worldwide in 2013 (WHO, 2014). Since its endorsement by the WHO in 1991, a combination of rifampicin, isoniazid, pyrazinamide and ethambutol or streptomycin during the first 2 months of treatment has remained part of the standard first-line TB treatment regimen globally (WHO, 1991). These guidelines are based on historic trials that assessed outcome during pulmonary TB treatment (Fox et al., 1999). TB drug regimens used for extra-pulmonary TB, including frequently fatal forms such as TB pericarditis and TB meningitis (TBM), follow the same principles but not guided by trials that assessed patient outcome. Inadequate TB drug exposure (as measured by pharmacokinetic/pharmacodynamic [PK/PD] parameters in blood) is associated with a poor clinical response, treatment failure and acquisition of drug resistance in pulmonary TB patients (Pasipanodya and Gumbo, 2011). It is intuitive to assume that reduced drug exposure in tissues due to inadequate drug penetration into extra-pulmonary disease sites may enhance these detrimental effects.

In this issue of *EBioMedicine*, Shenje and colleagues present findings of the first study to determine TB drug concentrations in pericardial fluid of adults with pericardial TB (Shenje et al., 2015). The study was divided into two phases: 1) a pilot study, during which rifampicin concentrations were determined in paired blood and pericardial fluid samples taken once only at various time points in 16 patients and, 2) an intensive phase, during which intensive pharmacokinetic blood and pericardial fluid sampling were performed over a 24-hour period in 11 additional patients. All participants received a standard fixed-dose-combination daily TB drug regimen, including rifampicin (600 mg), isoniazid (300 mg), pyrazinamide (1600 mg) and ethambutol (1100 mg). Penetration of rifampicin into pericardial fluid was poor; the ratio of rifampicin concentration in pericardial fluid to paired blood concentration was 0.19 ± 0.33 (mean $\pm$ SD) in the pilot study. Non-protein bound rifampicin concentration (indicating active rifampicin) in pericardial fluid was extremely low (<1 mg/L) in all patients, and the median peak concentration in pericardial fluid (performed in the intensive phase) was lower than the median minimum inhibitory concentration (MIC) determined for TB strains collected previously from the same setting. Previous studies in TBM similarly showed that rifampicin at doses of 10 mg/kg/day seldom reaches cerebrospinal fluid (CSF) concentrations exceeding the MIC (Donald, 2010).

Shenje and colleagues (Shenje et al., 2015) further report poor ethambutol penetration into pericardial fluid; both 0–24 hour area under the concentration–time curve ($AUC_{0-24\ h}$) and peak concentrations (C_{max}) were significantly lower in pericardial fluid compared to plasma, resulting in ethambutol concentrations also falling below the typical MIC. Pyrazinamide concentrations in pericardial fluid were similar to that in plasma. However, pyrazinamide is only active under acidic conditions and after adjusting the MIC according to the measured pH of pericardial fluid (7.34 ± 0.11), pyrazinamide peak concentrations were ~40-times lower than the pH-adjusted MIC. Of the four drugs tested, isoniazid was the only one to reach effective pericardial fluid concentrations. Likewise in TBM, the contribution of ethambutol during treatment is questionable as ethambutol has poor CSF penetration (Donald, 2010). Isoniazid and pyrazinamide are considered invaluable during TBM treatment as both penetrate well into CSF (Donald, 2010). However, adequate C_{max} concentrations proposed for pyrazinamide in TBM are based on findings of in vitro studies, healthy volunteers and pulmonary TB and have not been informed by the pH of CSF during TBM.

Taken together, these findings support future trials to investigate the utility of alternative drug regimens in patients with severe forms

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of extra-pulmonary TB, in whom inadequate drug penetration may contribute to poor outcome. There is increasing concern that the conventionally prescribed dose of rifampicin (10 mg/kg/day) is too low, both for treating pulmonary TB (van Ingen et al., 2011) and extra-pulmonary TB (e.g. TBM) (Te Brake et al., 2015). Higher-than-normal doses of rifampicin (up to 35 mg/kg/day), combined with the other standard-of-care drugs given for 7 days, appear to be safe, result in increased rifampicin exposure and associate with a greater estimated fall in bacillary load compared to doses of 10 mg/kg/day in pulmonary TB patients (Boeree et al., 2015). Furthermore, in a TBM trial rifampicin, administered intravenously at doses of ~13 mg/kg/day compared to oral doses of ~10 mg/kg/day, resulted in higher rifampicin exposure (as measured by plasma $AUC_{0-6\ h}$, plasma C_{max} and the highest concentration measured in CSF) which was, in turn, associated with increased survival during the first 2 weeks of TBM treatment (Te Brake et al., 2015). Mortality was not the primary outcome and the sample size was small ($n = 60$), but these results emphasize the need for bigger trials to assess the utility of higher doses of rifampicin given intravenously, in frequently lethal forms of TB. It further seems logical to consider alternative drugs with good drug penetration into the disease site (e.g. fluoroquinolones such as moxifloxacin and levofloxacin that show good penetration into CSF during TBM), for treating severe forms of TB. However, a recent study that investigated the spatial distribution of TB drugs in intact biopsied lung lesions from TB patients using a matrix-assisted laser desorption/ionization (MALDI) mass spectrometry suite reveals a caveat of such an approach (Prideaux et al., 2015). This study found that moxifloxacin, although present at higher concentrations in lesions (as measured in homogenized lesions) than in plasma, was inhomogeneously distributed within the lesions with poor penetration into acellular caseum where bacilli may reside. Although the study by Shenje and colleagues (Shenje et al., 2015) will undoubtedly advance knowledge in the field of TB drug PK/PD considerably, it is important to consider that drug concentrations in accessible fluid adjacent to primary disease sites, i.e. pericardial fluid, and CSF, may provide an incomplete picture of drug concentrations within affected tissue, i.e. pericardium and meninges, respectively. Optimistically we consider that technologies such as the MALDI mass spectrometry suite will be developed to assess TB drug distribution in tissues in vivo which will provide the next piece in the puzzle of TB drug PK/PD in all forms of TB.

Conflicts of Interest

The authors declared no potential conflict of interest relevant to this manuscript.

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