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Commentary

Linezolid for Treating Tuberculosis: A Delicate Balancing Act

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There is an urgent need for better regimens to treat drug-resistant tuberculosis (DR-TB). Treatment for multi-drug resistant tuberculosis (MDR-TB, defined as resistance to both isoniazid and rifampicin) has a success rate of only 64% (Falzon et al., 2013), is prolonged for up to 24 months, and is poorly tolerated. Treatment success for extensively drug-resistant tuberculosis (XDR-TB, defined as MDR-TB with additional resistance to fluoroquinolones and an injectable) is only 40% (Falzon et al., 2013).

The oxazolidinone antimicrobial linezolid, which is registered for use in Gram-positive bacterial infections, has potentially useful antimycobacterial activity. Two small randomised controlled trials (RCTs) of linezolid in patients with XDR-TB have shown improved rates of sputum culture conversion (Lee et al., 2012; Tang et al., 2015). However, linezolid is poorly tolerated in DR-TB. A meta-analysis of linezolid use in MDR- and XDR-TB showed that 35% of patients interrupted linezolid due to toxicity (Zhang et al., 2015). Linezolid causes reversible myelosuppression and neuropathy, both of which are mediated by a dose- and time-dependent inhibition of mitochondrial protein synthesis (De Vriese et al., 2006). Linezolid's cumulative dose-related toxicity is a particular problem for patients with DR-TB, who need prolonged therapy.

In a paper published in this edition of *EBioMedicine*, Song and colleagues (Song et al., 2015) monitored serial mitochondrial function (cytochrome *c* oxidase:citrate synthase activity ratio), and correlated this with both adverse events and trough linezolid concentrations in participants from their trial of linezolid in XDR-TB (Lee et al., 2012). The mitochondrial function assay they developed appears to be a useful surrogate marker of mitochondrial toxicity. Their finding of a 2 μg/mL cutpoint for linezolid trough concentrations for toxicity is an important contribution, which, if confirmed in other settings, could be useful for therapeutic drug monitoring of linezolid in DR-TB.

However, toxicity is only one component of therapeutic drug monitoring. We still do not know the optimal linezolid dose or concentrations associated with treatment efficacy in DR-TB. The most widely used linezolid dose in DR-TB is 600 mg daily, but many patients require dose reduction to 300 mg daily after developing toxicity. In a meta-analysis failure rates were almost fourfold higher with the 300 mg than the 600 mg daily dose (Zhang et al., 2015).

Pharmacokinetic/pharmacodynamic (PK/PD) analyses from the parent RCT of the study by Song and colleagues demonstrated that plasma concentrations of linezolid were above the minimum inhibitory concentration (MIC) for each participants' individual *Mycobacterium tuberculosis* isolate during the entire dosing interval for nearly all patients treated with 600 mg daily (Lee et al., 2012). However, nine of 25 patients treated with 300 mg daily had trough concentrations below the MIC; two of whom developed linezolid resistance. No association was found between the time to culture conversion and either the peak or trough concentrations of linezolid (Lee et al., 2012). The linezolid PK/PD targets for Gram-positive infections are a free area under the concentration–time curve (AUC) to MIC ratio of >100 and a time above MIC of >85% (McGee et al., 2009). A small population pharmacokinetic study of patients with tuberculosis reported that linezolid 600 mg daily achieved a free AUC/MIC ratio of >100, but time above MIC was only 63% (McGee et al., 2009). A PK/PD modelling study, using published data from linezolid studies performed in persons without tuberculosis, estimated that doses of 300 mg once daily, 300 mg twice daily, and 600 mg once daily were associated with median percent of time with free linezolid concentrations >2 times the MIC of 1 mg/L (the suggested threshold for development of linezolid resistance) of 56%–100%, 100%, and 78%–100%, respectively; and the median percent of time above a concentration > 3.36 mg/L (the suggested threshold associated with neurologic toxicity) was 20%, 55%, and 40%, respectively (Barry et al., 2014). Linezolid's toxicity threshold thus appears to be very close to the efficacy threshold for tuberculosis.

Clearly, much more work remains to be done before linezolid can be recommended for widespread use in DR-TB. The combined total of participants in both RCTs of linezolid for XDR-TB is only 106, and both trials were done in East Asia. There may be important host factors affecting toxicity and efficacy in other regions. The high proportion of DR-TB patients who develop cumulative dose-related toxicity on linezolid suggests that its use should be for a limited period of time in an intensive phase, like the aminoglycosides. The optimal dose and duration of linezolid remains to be determined, especially

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in combination with new anti-tuberculosis drugs like bedaquiline and delamanid. Prospective data evaluating both the concentration threshold associated with toxicity and the concentrations needed to maximize antimycobacterial activity when combined with other agents are needed in patients with DR-TB. Alternative oxazolidinones with potential for more favourable risk:benefit ratios also need to be explored for use in DR-TB. For example, tedizolid, which is active against *M. tuberculosis* (Vera-Cabrera et al., 2006), appears to have less mitochondrial toxicity than linezolid (Flanagan et al., 2015). Finally, implementing linezolid for DR-TB in resource-limited settings, where the burden is greatest, will require dramatic price reductions and training for toxicity monitoring. Therapeutic drug monitoring will be difficult to implement in these settings.

Disclosure

GM has acted as a consultant to Merck, who market tedizolid. CAB declares no conflicts of interest.

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