Individualising Therapy for "Drug-Sensitive" Tuberculosis

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For over 25-years the standard 4-drug, short-course, regimen of 6 months rifampicin (R) and isoniazid (H) supplemented by pyrazinamide (Z) and ethambutol (E) for the first 2 months has been established as the treatment for drug-sensitive tuberculosis (TB); and enshrined in all recent national and international guidelines. However, as drug susceptibility testing undergoes a shift to genotypic methods that offer the possibility of rapid drug susceptibility information for increasing numbers of drugs, the case for deviating from this standardised approach to a more individualised one is emerging. In particular, the routine use of ethambutol could be discontinued.

Central to the current, short-course regimen are the sterilizing actions of pyrazinamide and rifampicin. By the late 1980s randomised trials had demonstrated that these drugs in combination with isoniazid in a 6 month regimen (2HRZ/4HR) were sufficient to achieve a relapse rate of less than 4% which was not improved by addition of a fourth drug(1-3). The rationale for retaining a fourth drug has been largely as an insurance against undiagnosed isoniazid resistance, present in 8% of the world's TB cases (as rifampicin-sensitive, isoniazid-resistant disease), ensuring that at least 3 effective drugs are being provided in the intensive phase(4). However, the standard, 4-drug, regimen in those with isoniazid mono-resistance has been shown to lead to unacceptably high rates of treatment failure (11%) and acquired rifampicin resistance (8%), meaning that identifying isoniazid resistance and then modifying therapy remains critical(5). Recent WHO guidelines recommend these patients receive 6 months of 4 effective drugs (rifampicin, pyrazinamide, ethambutol and levofloxacin), though further trials in this area are needed(4).

The CRyPTIC consortium has recently published findings demonstrating that Whole Genome Sequencing (WGS) can be used to predict susceptibility to the first-line TB drugs(6). This has led to the UK, the Netherlands and New York State, suspending or planning to suspend phenotypic susceptibility testing for isolates predicted by WGS as sensitive; and it will only be a matter of time before other countries follow suit.

Recent work on the programmatic turnaround time in the UK has shown that drug susceptibility information by WGS is available within 8 days of receipt of a cultured isolate, substantially faster than phenotypic results(7). Although at present WGS is only performed following culture, in the near future it is likely that direct sequencing from sputum will reduce the turn-around time for susceptibility information to a matter of days from sample collection(8).

In most countries, over 90% of cases of tuberculosis are susceptible to the 4, first-line drugs, hence ethambutol for these individuals will not provide any additional benefit and may contribute to harm, health service costs and drug resistance. Ethambutol can add a further 2-5 tablets to the daily pill burden if the 4-drug fixed-dose combination (FDC) is not used, and can have an unpleasant metallic taste. Both pill burden and adverse effects are significant contributors to regimen non-adherence. Optic neuritis is a relatively uncommon complication of ethambutol particularly at the 15mg/kg dose; however, the visual screening conducted at baseline contributes to health service burden. In addition, although the regimen cost for drug-sensitive TB is low, depending on the FDC used, ethambutol can contribute up to 60% of the drug cost of the intensive phase of therapy.

However, perhaps the most compelling case for the rational use of ethambutol is drug resistance. Recent surveys suggest up to 65% cases of multi drug-resistant (MDR) TB (resistant to at least rifampicin and isoniazid) are also resistant to ethambutol(9). Ethambutol resistance is driven by exposure to the drug as part of the primary regimen, limiting its utility in the management of MDR-TB. Therefore, a more rational use of first line drugs now, could potentially lead to increasing options for the management of future drug-resistant TB.

As diagnostics improve, there is a strong case for using drugs more wisely. At present over 90% of people are over-treated with the first-line regimen, whilst there is systematic under-treatment of patients with isoniazid mono-resistance, particularly in settings reliant on Xpert-MTB/RIF (which is unable to detect isoniazid mono-resistance, and has in some places led to a reduction in phenotypic drug susceptibility testing). As complete first-line susceptibility predictions are available ever more rapidly and widely, we need to reflect on the rationale for our current treatment approach, and adapt our practice and guidelines. Prompt cessation of ethambutol once first-line drug susceptibility is predicted would benefit patients and health systems now. As direct-from-sample sequencing, or alternative methodologies, start to deliver more rapid prediction of susceptibility and resistance to all first-line drugs, further opportunities to initiate truly individualised therapy, and realise yet more benefit, will arise.

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