Finding the right dose of rifampicin, and the right dose of optimism

After the widespread introduction of rifampicin in the early 1970s, it took another two decades, and more than 50 randomised trials with more than 20 000 participants to finalise the drugs, doses, and schedule for the currently recommended regimen for newly diagnosed patients with active tuberculosis. Yet this regimen has important drawbacks, most notably the 6 months duration, and frequent toxicity. These limitations have stimulated considerable research interest to find shorter and better-tolerated regimens.

New drug development is expensive, and progress in the past 20 years has been very slow. Investigators have re-examined current drugs and doses, including the dose of rifampicin, which was initially selected as the lowest effective dose because this drug was very expensive when first introduced. Bacterial clearance in mice, extended early bactericidal activity in patients with pulmonary tuberculosis, and 6-month survival in patients with tuberculosis meningitis have all been improved with higher doses of rifampicin. In patients with tuberculosis, meningitis survival was closely related to serum concentrations. In the Lancet Infectious Diseases, Martin Boeree and colleagues report findings of a randomised controlled phase 2B trial of patients with drug-sensitive pulmonary tuberculosis. The trial assessed four experimental regimens given for 12 weeks followed by 14 weeks of isoniazid and rifampicin. The regimen with rifampicin dosage of 35 mg/kg (RIF35) resulted in faster time to culture conversion compared with the standard regimen. This difference was not seen with the other experimental regimens (including two with rifampicin dose of 20 mg/kg), and was seen only with liquid culture media, but not solid cultures. Compared with the standard regimen, serious adverse events including hepatitis were not significantly higher with any experimental regimen, although the study was underpowered for this outcome, and the occurrence of hepatitis with RIF35 was more than twice as high as with standard rifampicin doses.

There are two important methodological issues to consider when interpreting this interesting and well executed study; use of the innovative multi-arm, multi-stage (MAMS) design, and time to culture conversion as the primary outcome. The MAMS trial design has been used successfully in phase 2 cancer trials to select regimens for phase 3 trials, and to minimise enrolment to regimens with inadequate efficacy or excessive toxicity. However, to successfully reduce the number of participants enrolled to worse regimens, the time from enrolment to outcome in participants included in the interim analyses must be substantially shorter than the total time to enrol all participants. In this trial, 117 participants were randomly assigned to the arms that were stopped early, compared with 127 randomly assigned to the experimental arms that were continued—the difference represented a 3% reduction of overall enrolment—a rather modest benefit.

The other consideration is the critical importance in phase 2 trials of the predictive accuracy of the intermediate outcome, and a high negative predictive value is essential to avoid falsely concluding that a regimen is inadequate. In this trial, enrolment was stopped for two regimens containing SQ109, based on the time to culture conversion. But, before concluding that SQ109 should not be considered for phase 3 trials, what is the accuracy of this outcome? Using meta-regression techniques, Wallis and colleagues found a relationship between 2-month culture conversion (a dichotomous outcome) and relapse. This spurred highly optimistic thinking about the value of phase 2b trials, since dampened by the failure of 4-month fluoroquinolone-containing regimens to achieve relapse free cure in three independent trials, despite promising culture conversion data. We advocate for continued study of SQ109, since Wallis and colleagues did not estimate negative (or positive) predictive values, nor did they examine the relationship of relapse free cure with time to culture conversion, the outcome used in this trial.

We believe that a shorter regimen for active tuberculosis that is also safe and well tolerated is urgently needed. Phase 2 trials can be helpful to identify promising regimens, but the intermediate outcome of 2 or 3 months culture conversion requires...
further validation work, before we can confidently use this outcome to plan phase 3 trials. This work would also allow use of the more efficient MAMS design.

Boeree and colleagues are very optimistic that high dose rifampicin might be useful in shortening current treatment for drug sensitive tuberculosis; we share their optimism, but in a more limited dose.

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RR reports that one of the authors of the paper, Rob Aarnoutse, was a former PhD supervisor and continues to be a collaborator.

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