Pound foolish and penny wise-when will dosing of rifampicin be optimised?

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In September, 2017, the authors attended a tuberculosis conference in China where it became clear that resistance to anti-tuberculosis drugs could render the ambitious WHO targets for tuberculosis elimination unreachable.

The authors believe that the tuberculosis community should act swiftly and make smart and well founded choices to improve treatment success. Excellent studies have been published on optimal approaches to treat resistant tuberculosis, but unfortunately the tuberculosis community is transforming this knowledge into recommendations that change standard therapy at a slow pace. Effective interventions are needed more urgently than ever if the goals of the End TB Strategy are to be achieved. In 2013 and 2014, WHO made the courageous decision of making bedaquiline and delamanid available to the global community. This occurred at an early investigational stage when evidence from phase 3 trials was still absent; before that, bedaquiline and delamanid could not be included in standard therapy.

Although studies have shown that the dosing regimen for rifampicin currently recommended in all international guidelines is suboptimal,[1-4] a high-dose treatment strategy has still not been recommended; rather, the scientific community requested more studies.

The tuberculosis community's focus on a once daily, 600 mg dose of rifampicin is worrisome. This dose is at the low end of the dose–response curve and was selected in the past mainly for financial reasons.[2] Comparing the strength of evidence for the efficacy and safety of bedaquiline and delamanid, the authors do not understand why the demands of the scientific community are so much higher for a change in dosing of rifampicin (an old drug), when multiple studies have shown already that it is safe and more efficacious.

In vitro and in vivo pharmacokinetic and pharmacodynamic studies support a higher dosing strategy for rifampicin.[5-7] Bacteriological studies also indicate that the use of the standard once daily, 600 mg dose of rifampicin can increase the number of new multi-drug resistant tuberculosis cases, especially in case of isoniazid monoresistant strains or the Beijing genotype of *M tuberculosis*, both of which might be more tolerant to rifampicin than other strains.[8] Moreover, two phase 2 studies showed favourable outcomes with high-dose rifampicin ranging from 10 to 35 mg/kg orally per day in the absence of any relevant toxicity.[1,9,10] In Indonesian patients with tuberculous meningitis, high intravenous doses (about 13 mg/kg) of rifampicin yielded a 50% reduction in mortality.[11] Therefore, why not reassess the original data[2] to make an evidence-based decision to recommend a high dose of rifampicin in tuberculosis treatment?

The ambition of WHO to eliminate tuberculosis between 2035 and 2050 requires effective interventions and our suggestion could be one of them. The most important first-line drug against tuberculosis is underdosed and we suggest taking a firm decision to change this situation.

It is time for the rapid programmatic introduction of a high dose of rifampicin (30–35 mg/kg, which a phase 2 trial indicated would improve efficacy)[1,9] for at least four high-risk groups that are not well treated by the standard dose—ie, patients with tuberculosis meningitis, HIV, diabetes, and severe illness characterised by a low body mass index (<18 kg/m^2). These patients are characterised by high rates of absorption problems, acquired drug resistance, relapses, and mortality. The decision to increase the dose of the first-line tuberculosis therapy and prevent further development of resistance should not be postponed.

A rapid roll-out of high-dose rifampicin in these high-risk groups should be organised in a centrally controlled way, similar to the WHO bedaquiline and delamanid roll-out. A large phase 3 trial of higher dose rifampicin (20 and 30 mg/kg) is underway (NCT02581527).[3] Although results will only be available in 3–5 years, phase 3 trials will provide much needed data to optimise the duration of first-line treatment.

Introduction should be accompanied by appropriate monitoring according to the US Food and Drug Administration, European Medicines Agency, and WHO guidelines for early market release of drugs. Because rifampicin, unlike bedaquiline and delamanid, is already off-patent, we call on WHO, the American Thoracic Society, and the European Respiratory Society in consultation with the US Food and Drug Administration and European Medicines Agency, to act quickly.

In our opinion, saving pennies on a 600 mg, once daily, rifampicin dose while losing lives of patients with tuberculosis, does not pay off.

We declare no competing interests.

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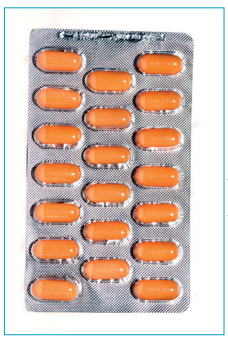

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