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Conflicting Findings on an Intermediate Dose of Rifampicin for Pulmonary Tuberculosis

To the Editor:

Velásquez and colleagues studied rifampicin up to a dose of 20 mg/kg/d in Peruvian patients with pulmonary tuberculosis (TB) (1). In their per-protocol analyses they found a significant decrease in viable colony-forming unit counts of *Mycobacterium tuberculosis* with each 5 mg/kg increase in rifampicin dose and with each log increase in rifampicin area under the plasma concentration–time curve from 0 to 6 hours (AUC_{0-6}), but not with each log increase in AUC_{0-6}/minimum inhibitory concentration for 99.9% of *Mycobacterium tuberculosis*. The authors suggest the continued investigation of higher doses of rifampicin, also beyond 20 mg/kg.

These results seem to contrast with our very similar double-blinded, randomized, placebo-controlled, phase II clinical trial performed in patients with pulmonary TB in Tanzania (HIGHRIF2 [2]). In that study, we combined 600 mg (∼10 mg/kg), 900 mg (15 mg/kg), and 1,200 mg (20 mg/kg) rifampicin with standard doses of isoniazid, pyrazinamide, and ethambutol, administered daily for 2 months. However, we did not observe significant differences between arms in bacteriological response, as quantified by time to culture conversion in mycobacteria growth indicator tube and Löwenstein-Jensen, and in the change in bacillary load over time, as measured by time to positivity in MGIT and colony-forming units on Middlebrook 7H11 plates. Most likely this was due to a lack of power for bacteriological endpoints, large interpatient variability in exposures and overlapping exposures between the dose groups (although our pharmacokinetic–pharmacodynamic analysis revealed no relationship either), and/or because the steep part of the exposure–response curve had not yet been reached (2). We assume that the different findings in Velásquez and colleagues's study and ours can be explained by the limited number of patients with exposure data in our study, the more powerful approach to the analysis of bacillary elimination and pharmacokinetic–pharmacodynamic relationships as performed by Velásquez and colleagues using nonlinear mixed effects modeling, and/or the differences in the patient populations examined.

The authors state that theirs is the first controlled study to show the effects of both dose and exposure responses of rifampicin on sputum sterilization. Apart from HIGHRIF2, we have performed a phase II multiple dose rising study (HIGHRIF1) in which we studied a much higher dose of rifampicin: up to 35 mg/kg of rifampicin daily for 2 weeks (3). A greater decrease in bacterial load was observed in the higher dosing groups (3). From the same data, a significant exposure–response relationship between rifampicin exposure and early bactericidal activity could be derived. Clinical trial simulations showed greater early bactericidal activity for 50 mg/kg rifampicin (4). Evaluation of the pharmacokinetics, early bactericidal activity, and safety of 50 mg/kg rifampicin in patients with pulmonary TB is currently ongoing. In another recent study, PanACEA-MAMS-TB-01, a daily rifampicin dose of 35 mg/kg, administered over 12 weeks together with standard doses of isoniazid, pyrazinamide, and ethambutol, was able to decrease the time to culture conversion. Of note, the 8-week adjusted hazard ratio of 2.06 in this trial is the highest reported for any TB regimen so far (5). In an exposure–response analysis of the same data, increasing rifampicin exposure shortened time to sputum culture conversion, and the effect did not plateau, indicating that doses of >35 mg/kg could be even more effective (6). In summary, investigation of further increased doses of rifampicin beyond 20 mg/kg daily, as recommended by Velásquez and colleagues, is already taking place. ■

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Reply to te Brake *et al.*

From the Authors:

We thank te Brake and colleagues for their interest in the HIRIF (Evaluation of High-Dose Rifampin in Patients with New, Smear-Positive Tuberculosis) trial results (1, 2) and for the PanACEA (Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics) consortium's ongoing commitment to optimize rifampin dosing for patients with tuberculosis. te Brake and colleagues highlight a perceived difference between the HIRIF findings and those of HIGHRIF2 (PanACEA HIGHRIF study 2) (3). The direction and magnitude of the effects observed in both trials were similar: HIGHRIF2 showed a nonsignificant trend toward a higher hazard of culture conversion in both mycobacteria growth indicator tube and Löwenstein-Jensen medium for the 1,200 mg dose compared with the 600 mg dose, and HIRIF revealed that higher rifampin doses and exposure resulted in modest and statistically significant increases in the rate of sputum culture sterilization (2). Interpretation of the two studies is consistent: rifampin doses up to 20 mg/kg/d, with no additional changes to the regimen, are unlikely to permit treatment shortening.

Similarly to HIGHRIF2, HIRIF found no difference in the secondary efficacy outcome of 8-week culture conversion in Löwenstein-Jensen medium with daily rifampin doses up to 20 mg/kg. Rifampin doses also did not influence the frequency of treatment failure and disease recurrence at 12 months. HIRIF was not powered for these secondary endpoints, which would have required a much larger sample size than was possible for a phase II trial. We are encouraged by the advances the PanACEA consortium has made to date in optimizing doses of rifampin higher than 20 mg/kg/d. We also look forward to improving the statistical power for efficacy and safety evaluations by pooling HIRIF and HIGHRIF2 data through collaboration with the authors of the correspondence. Combined with ongoing trials to optimize the dose of rifampin, pooled individual-level patient data analyses will be critical to influence future treatment guidelines and improve the lives of patients with tuberculosis. ■

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