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### Conflicting Findings on an Intermediate Dose of Rifampicin for Pulmonary Tuberculosis

To the Editor:

Velázquez 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 (AUC0–6), but not with each log increase in AUC0–d, 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 Velázquez and colleagues’ 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 Velázquez 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 2.03 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 Velázquez and colleagues, is already taking place.

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Supported by PanACEA, which is part of the EDCTP2 program supported by the European Union (grant number TRIA2015-1102-PanACEA).

Originally Published in Press as DOI: 10.1164/rccm.201811-2101LE on January 15, 2019

Author disclosures are available with the text of this letter at www.atljournals.org.
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Supported by National Institute of Allergy and Infectious Diseases/NIH grants U01 AI091429 (C.D.M. and G.R.D.) and L30 AI120170 and UM1 AI068636 (G.E.V.). G.E.V. received support from the Ronda Stryker and William Johnston Fellowship in Global Health and Social Medicine and the Dr. Lynne Reid/Drs. Eleanor and Miles Shore Fellowship at Harvard Medical School, the Burke Global Health Fellowship at the Harvard Global Health Institute, and the AIDS Clinical Trials Group Minority HIV Investigator Mentoring Program. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or the institutions with which the authors are affiliated.

Originally Published in Press as DOI: 10.1164/rcmm.201812-2281LE on January 15, 2019

Author disclosures are available with the text of this letter at www.atsjournals.org.

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