

Reply to “Contradictory Results with High-Dosage Rifamycin in Mice and Humans”

Eric L. Nuermberger,^{a,b} Ian M. Rosenthal,^a Rokeya Tasneen,^a Charles A. Peloquin,^c Khisimuzi E. Mdluli,^d Petros C. Karakousis,^{a,b} Jacques H. Grosset^a

Center for Tuberculosis Research, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland^a; Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland^b; Infectious Diseases Pharmacokinetics Laboratory, College of Pharmacy, and Emerging Pathogens Institute, University of Florida, Gainesville, Florida^c; Global Alliance for TB Drug Development, New York, New York^d

We thank Coates and colleagues for their interest in our recent paper demonstrating in two pathologically distinct murine models of tuberculosis (TB) that rifapentine (RPT) is approximately 4 times more potent (on a mg/kg body weight basis) than rifampin (RIF) when used alone and in combination with other first-line drugs (1, 2). Like us, Coates et al. were struck by the apparent contradiction between these results and the results of a recent clinical trial in which replacement of RIF with RPT (each drug given daily at a dose of 10 mg/kg body weight) did not significantly increase the proportion of TB patients (2-month sputum cultures) converting to negative result (1, 3, 4). In an effort to explain the differing results, they assert that (i) RIF-tolerant bacterial persisters in human TB have different susceptibility to rifamycin drugs and that dosing regimens that produce higher peak concentrations (maximum concentration of drug in serum [C_{max}]) eliminate persisters more rapidly than those producing lower peaks irrespective of the area under the concentration-time curve (AUC) and that (ii) mouse models do not harbor rifamycin-tolerant persisters because the incubation period between infection and treatment is too short for them to appear, and that, under such conditions, the AUC/MIC ratio is the more predictive pharmacodynamic parameter (1). As evidence to support the first of these assertions, Coates et al. state that “the move from weekly dosage with RPT to daily dosage greatly increases the AUC with consequently increased sterilizing activity in the mouse, but the peak concentrations are little altered, with consequent failure to increase efficacy in humans” (1). However, while it is clear that the sterilizing activity of RPT-containing regimens increases with total weekly dosage and would appear to be more closely linked to AUC rather than C_{max} in mice (5–8), the relationship between pharmacodynamic parameters and efficacy in humans has, to our knowledge, never been tested for any rifamycin. It certainly was not tested in Tuberculosis Trials Consortium (TBTC) study 29 (3).

We also respectfully disagree with the second assertion by Coates et al. that the duration of infection in mice is not long enough to produce RIF-tolerant persisters. Our position is supported by several lines of evidence. First, the treatment of mice 5 days per week with the first-line regimen, including serum RIF exposures which are at least as high as those attained in humans, typically requires drug administration for 3 to 4 months to render mouse lungs culture negative and 5 to 6 months to prevent relapse after treatment discontinuation (6–11). If the infecting bacilli were not tolerant to the action of RIF, much shorter durations of treatment should be possible. Second, increasing RIF and RPT doses shortens the duration of treatment needed to attain the same endpoints, indicating more rapid eradication of some RIF-

tolerant persisters (2). However, pushing RPT doses from 5 to 320 mg/kg (with nearly dose-proportional increases in exposure) in similar regimens is still not sufficient to prevent relapse in mice after 4 weeks of treatment (12). Finally, prolonging the duration of infection prior to treatment from 2 weeks to 6 weeks (a duration long enough to produce RIF-tolerant bacilli in the authors' *in vitro* models [13]) did not result in longer durations of treatment necessary to render mice culture negative or to prevent relapse in the present study (2). Together, these data indicate that infected mice harbor persisters tolerant to very high rifamycin exposures. In order to better understand the relationship of preclinical models to early and late outcomes in human TB, we believe that, rather than determining “how long it takes for persister populations to appear in chronic murine tuberculosis” (1), we need to better characterize and directly compare persister populations in human sputum samples and common preclinical models in terms of overall size, proportion of the total bacillary burden, extent of drug tolerance, and relevant gene expression, proteomic, and metabolomic signatures. Until then, we fully support the efforts under way to evaluate higher doses of both RIF and RPT in clinical trials (3, 14–16) and will continue to advocate that the rifamycin best suited for clinical use is that which produces the greatest sterilizing efficacy at the highest well-tolerated dose.

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Address correspondence to Eric L. Nuermberger, enuerm@jhmi.edu.

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