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Simplifying Rifapentine Dosing for Tuberculosis Treatment and Prevention

In this issue of the *Journal*, Hibma and colleagues (pp. 866–877) convey results of a population pharmacokinetic (PK) model for rifapentine based on a meta-analysis of participant-level PK data from nine clinical trials (1). These data are both relevant and timely, as evidence on the use of rifapentine for both tuberculosis (TB) treatment and prevention continues to build. Rifapentine efficacy for TB prevention was first shown in a trial of a 3-month regimen of weekly rifapentine and isoniazid (3HP; PREVENT-TB trial) and more recently in the BRIEF-TB trial, in which a 1-month daily rifapentine and isoniazid (1HP) regimen in people living with HIV was as effective as 9 months of daily isoniazid (2–4). Investigations into rifapentine use in TB treatment include an ongoing phase 3 clinical trial, the Tuberculosis Trials Consortium (TBTC) Study 31, in which rifapentine-containing regimens are being studied with the goal of shortening treatment duration to 4 months for drug-susceptible TB (5).

The excellent work by Hibma and colleagues demonstrates how models built on a robust set of pharmacology data, strengthened by inputs from multiple studies and validated by external data sets, can be utilized to inform current dosing recommendations as well guide future clinical trial design. One of the article's primary conclusions suggests that weight-based dosing of rifapentine is unnecessary, and in the authors opinion, "puts the smallest, most vulnerable individuals at risk of underexposure and, consequently, treatment failure" (1). The second major finding was that people living with HIV may require a higher dose of rifapentine compared with individuals without HIV. It is unclear as to why people with HIV have reduced rifapentine exposures, but this may lead to worsened outcomes based on rifapentine exposure–response relationships during TB treatment. However, one of the limitations of the analysis by Hibma and colleagues was the relatively low number of people with HIV included in the analysis, making up only 81 of the 863 participants. These data could be strengthened by the inclusion of PK data from BRIEF-TB, when available.

The understanding of rifapentine's pharmacology has advanced since the drug was initially U.S. Food and Drug Administration approved in 1998. Early phase one healthy volunteer studies suggested rifapentine did not induce (or increase) its own metabolism (6), which is refuted in the present work by Hibma and colleagues. By combining rifapentine PK data from nine clinical trials, the authors' population rifapentine PK model predicts the clearance of rifapentine increases 73% after repeated daily dosing, ultimately stabilizing by Day 21. Furthermore, the authors report a concentration effect on rifapentine autoinduction, which follows an maximum effect (Emax) relationship, with the greatest effect at daily doses of 300 mg, whereas the extent of autoinduction appears to plateau at doses above this amount. Conversely, intermittent dosing of rifapentine showed only minimal to moderate metabolism autoinduction.

Collectively, these new findings have implications for current treatment narratives as well as rifapentine dosing in future trials and represents a significant step forward for the field. Beginning with the implementation of the 1HP regimen, the Hibma and colleagues data

Originally Published in Press as DOI: 10.1164/rccm.202006-2144ED on July 7, 2020

support that a flat dose of rifapentine 600 mg is likely better for all individuals 13 years of age and older, regardless of weight. This is in contrast to rifapentine dosage studied in the BRIEF-TB trial of 1HP, in which rifapentine was stratified by weight, approximated at 10 mg/kg, with a maximum dose of 600 mg daily (3). It is less clear where the authors believe the weight breakpoint, if any, exists for flat dosing with 3HP. The lower limit of current 3HP dosing recommendations is 10 kg in individuals 2 years or older and guidelines recommend a weekly dose of 300 mg rifapentine (7). The Hibma and colleagues analysis does not specifically address individuals at the very low end of this weight band dosing, and more investigations may be needed in this population before recommending an increased or flat dose of rifapentine for 3HP.

Next, this new rifapentine PK data should inform clinicians and guidelines as to the potential need for a higher dose of rifapentine in people living with HIV. The authors recommend "at least 30% higher doses to achieve equal drug exposures to HIV-negative persons" (1). Given the current 150 mg formulation of rifapentine, one could imagine a daily dose of 750 mg rifapentine in the 1HP regimen or a 1,200 mg weekly dose of rifapentine for 3HP for people with HIV. Again, this would represent a significant increase in dose for individuals at the low end of the approved weight bands, and safety analyses should be conducted prior to widespread implementation. It must be noted that exposure–response targets for rifapentine are still lacking for TB prevention; however, given the low rates of the primary outcome of TB and mortality in BRIEF-TB and PREVENT-TB, one could argue efficacy thresholds are being met with the current dosing schemes, including in individuals living with HIV.

Finally, a note about what remains to be studied with respect to rifapentine pharmacology, it is not fully understood what effect, if any, antiretrovirals have on rifapentine PK. PK data from the BRIEF-TB study may give insight into what effect an enzyme-inducing drug, such as the antiretroviral efavirenz, has on rifapentine PK. As the analysis by Hibma and colleagues only included one TB-prevention trial, and none that included individuals receiving antiretrovirals, additional studies are needed to bolster findings of the current analysis. Next, previous reports have shown a pharmacogenomic (PG) influence to rifapentine PK (8), an ongoing PG analysis within the BRIEF-TB study will give insight into whether flat dosing of rifapentine is appropriate for TB prevention across all genetic populations. Last, results from TBTC Study 31, which utilizes a dose of 1,200 mg rifapentine in all participants, is expected in October 2020 and will inform on TB treatment outcomes in both individuals with and without HIV coinfection. These results will help our understanding of exposure–response relationships for rifapentine in TB treatment. An additional PG analysis in Study 31 will inform the field on both the efficacy of rifapentine-based regimens across broad genetic groups and assist in continuing to piece together PG influences on rifapentine PK.

Together with completed and ongoing clinical trials, the data presented by Hibma and colleagues continue to move rifapentine use forward in TB prevention and treatment. The simplified dosing strategies proposed may help drive generic formulations of rifapentine, ultimately bringing down the cost associated with rifapentine use. Ultimately, the goal is to bolster rifapentine approval in high TB burden countries where its implementation and utilization could make a large impact on global TB burden. ■

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

Acknowledgment: The author thanks Drs. Susan Swindells and Kimberly Scarsi for their thoughtful discussion and review of this commentary.

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