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Modeling Treatment of Latent Tuberculosis: Shortening the Leap of Faith?

In the 64 years since preventive therapy for latent tuberculosis (TB) was first pioneered by Comstock and colleagues in Alaska, impressive treatment shortening has been achieved with two simple drug classes: isoniazid and rifamycins. In the last decade, the duration of therapy for latent TB infection (LTBI) has progressively decreased, going from 9 months to 3 to 4 months, and perhaps to 1 month. To guide these advances and design phase 3 prevention trials, investigators have designed and tested regimens of antimicrobial treatment in the chronic low-dose mouse model. Inconveniently, mice do not develop latent TB. Thus, to estimate drug/regimen efficacy, researchers have assessed rates of bacterial burden decline in mice as a surrogate for LTBI efficacy, coupled to a leap of faith.

In this issue of the *Journal*, Foreman and colleagues (pp. 469–477) now present a dramatic animal study suggesting that the novel 3-month 12-dose isoniazid–rifapentine (3HP) regimen for preventive treatment of LTBI has sterilizing capacity (1). For the TB world, these are impressive findings; validation of these findings in other, related settings would provide important support for the large-scale use of such interventions. Scale-up of this intervention is already underway in both low-burden (2) and high-burden/high-HIV settings (3), so the short-term validation may be soon achieved.

There are important strengths to the study, and there are important questions remaining. The study was performed in a well-documented nonhuman primate model (the rhesus macaque) in which the pathophysiology of tuberculosis appears to recapitulate the human analog well. In the particular model employed here, low-dose infection with *Mycobacterium tuberculosis* (MTB) leads to a state of chronic infection; in their study, rapid progression to active disease occurred in 2 of 16 animals, whereas the remaining 14 remained stable with minimal or no signs of active disease. In a classic approach, 3 months after infection, half the remaining infected animals were treated with the 3HP regimen administered in feed, and half received no treatment. At 7 months after infection, all animals received an infectious intravenous dose of simian immunodeficiency virus, leading to a well-recognized state of immune impairment in this host. High simian immunodeficiency virus viral loads were documented. After a 3-month period of observation, all surviving animals were killed, and multiple tissues (including lung, bronchial lymph nodes, liver, spleen, and kidney) from all 14 were cultured on solid media. Cultures were positive in all untreated animals, whereas only one culture from one of seven treated animals yielded a single colony on one plate. These results are indeed dramatic. On their surface, they may indicate that short-course rifamycin-based regimens for LTBI are highly sterilizing; in that case, the wide application of such regimens could presage a major step forward in TB prevention and control.

We have two sets of questions that help to place these results in perspective, and that temper these hopes with scientific caution. Our first questions concern the extent to which this model replicates the human response to MTB. The authors cataloged clinical parameters including tuberculin skin test conversion and chest X-ray scoring, as well as body weight and temperature, throughout the experiment. And as one would expect to see in humans, tuberculin skin test conversion occurred in the majority of animals by 30 days and in all of the animals by 70 days, and serial chest X-rays were essentially negative throughout until the reactivation phase. Importantly, the postmortem pathology observed in the nonhuman primates closely paralleled that of humans.

Our second set of (related) questions concerns exactly what biological state is being modeled. In recent years, there has been increasing evidence that TB infection exists in humans not as a

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binary condition, of latent TB infection versus active TB disease (4), but rather as a spectrum that extends from latent, quiescent infection, perhaps residing only within selected sites or cell lines, to incipient and subclinical disease (5), to active TB disease (6). More specifically, one must ask whether the condition being treated in these rhesus macaques is representative of truly persistent/latent infection, whether it is more similar to subclinical disease, or whether it is parallel to the human state in the first year after infectious exposure. The importance of this question is readily apparent: If true persistence is not resolved, then the long-term risk of reactivation has not been eliminated, and the efficacy of the intervention, although still significant, may be less than what we hope. In this regard, we wonder whether the results of this study indicate actual sterilization of MTB in the host animals. To address some of this concern, the authors performed BAL before giving 3HP and documented culture-negativity. Nevertheless, our concerns arise from two considerations: first, numerous authors have presented evidence that persistent MTB bacilli are notably challenging to cultivate, and that large numbers of bacilli that are nonculturable with routine solid media can be recovered if specimens are cultured in liquid media after adding culture filtrates or resuscitation promotion factors (7, 8); and second, the sensitivity of culture using solid media has low but important limits. It is to the authors' credit that multiple tissues were examined for acid-fast bacilli and that multiple tissues were cultured; recent work has suggested that lymph nodes may represent sites of likely persistence (9).

The careful work by Foreman and colleagues represents an important addition to our understanding of latent TB infection; evaluation of the current scale-up efforts will contribute importantly to our understanding of the limits of the model. ■

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