Of Mice and Men, Women, and Children: Using Animal Models to Inform Tuberculosis Clinical Trials of Novel Agents

In this issue of the *Journal*, Kaushik and colleagues (pp. 570–579) report on another iteration of the Grosset murine model of treatment for latent tuberculosis infection (LTBI) (1). Over decades, the utility of this model has been remarkably impressive. It convincingly demonstrated the therapeutic potential of three different short regimens: 2 months of rifampin and pyrazinamide, the 12-dose isoniazid/rifapentine regimen (3HP), and the 1-month isoniazid rifapentine regimen in patients with HIV infection (1HP). Each of those regimens subsequently appeared to succeed in large phase 3 trials. In this model, inbred mice are immunized with an aerosol challenge with bacillus Calmette-Guérin (BCG) and then infected with virulent *Mycobacterium* tuberculosis, leading to establishment of a low-level infection that remains stable and nonlethal for months. Although the mouse model is limited in informing us in the domain of safety, it does identify regimens worthy of testing in humans. Many experienced investigators believe that no regimen should be tested in humans that has not demonstrated potential for success in this murine model.

In the domain of LTBI, however, the model provides a measure with which we can compare regimens that have succeeded in humans with new untested regimens that could offer major advantages. The first such study, performed in Paris, demonstrated the relative advantage of 2 months of rifampin and pyrazinamide and 3R over 6 months of isoniazid (6H), although no regimen was fully sterilizing (2). A subsequent study in the same model suggested the efficacy of the once-weekly 3HP regimen for LTBI (3). The 3HP regimen was later confirmed in multiple trials and studies (4, 5), although the model could not predict the continued low-level occurrence of generally mild hypersensitivity reactions in humans, which occasionally limit the use of this regimen (6). A decade later, the model suggested the efficacy of a regimen of rifapentine with or without isoniazid for 4–8 weeks (7, 8). The BRIEF TB trial in persons with HIV infections in high burden settings, based on that mouse work, has supported the efficacy of the 1HP regimen (9). More recently, we are beginning to learn more by "modeling the modeling;" sophisticated mathematical modeling of observations from the mouse model has begun to illuminate a small part of the unknown space between tuberculosis (TB) infection and TB disease (10). Such efforts suggest that one important variable is the size of the infectious dose. Perhaps such efforts will help us to understand why treatment of LTBI sometimes fails and whether it is reasonable or quixotic to imagine that treatment of LTBI might have a lifelong effect (11).

The same group has spent considerable effort seeking a role for bedaquiline (BDQ) in the management of LTBI. BDQ's long half-life and demonstrated potency make it an attractive potential foundation for LTBI treatment. An earlier LTBI model study by this group found similar efficacy for 2 months of daily rifapentine with or without isoniazid; efficacy was lower but substantial for 4 months of rifampin alone, 3 months of rifampin and isoniazid, 3 months of once-weekly isoniazid/rifapentine, or 1 month of BDQ plus rifapentine (8). The increasing interest in long-acting injectable (LAI) formulations as a means to improve adherence and diminish demand on health services has stimulated investigation of this format for BDQ. An assessment of bactericidal activity of LAI forms of BDQ indicated prolonged activity (at least for 12 wk), but bactericidal potency was less than seen with daily oral regimens (12).

In a creative next effort reported in this issue of the *Journal*, the authors have investigated the performance of regimens combining oral and LAI formulations (1). Moreover, they combine bactericidal assessments with pharmacokinetic evaluation and determination of sterilizing effect. The design is thus inventive, strong, and complex. The study assessed 12 different treatment arms (mostly with 2-wk durations) for bactericidal activity and 8 arms for sterilizing activity, all at multiple time points followed to week 28. Key findings were that *1*) all oral-only regimens were less bactericidal than the same regimens in combination with one or two doses of LAI BDQ and *2*) the most sterilizing regimens (by far) were oral BDQ with two LAI doses at weeks 0 and 4 or oral BDQ plus rifapentine with one LAI dose at week 0.

There are limitations of this study: The follow-up period was lengthy, bordering on the period of reliability for the model; there was only one true "control" regimen (1HP), which was tested infrequently and performed more poorly than expected (thereby demonstrating the hazards of "biocreep" [13]); safety issues such as the risk of drug interaction leading to excessive levels of the QT-influencing M1 metabolite (14) cannot be reliably assessed in the mouse; 8 of the 501 BALB/c mice were lost to cage flooding; Kramnik mice (15) were used to quantitate BCG implantation, which was initially low, forcing some delay in initiation (*see* the METHODS section in the online supplement); drug levels were measured in Belgium with BALB/c mice from Germany rather than the United States; and the initial BCG infection required adjustment to achieve proper dosing. Nonetheless, the fundamental parameters of the model (e.g., baseline bacillary load, stability of bacillary load in untreated animals) were respected, which supports confidence in the findings, and the limitations were faithfully reported by the investigators in great detail. An important challenge is that sterilization was assessed at 28 weeks, a change from all prior studies that assessed this at 3 months after the end of treatment. However, all regimens were assessed in the same way, enabling meaningful comparisons.

The value of this work is substantial, with several important implications. First, these are creative combinations using mixtures of drugs, doses, and routes of administration. In the clinical arena, we have been poorly imaginative about how we might effectively use the tools we have, and this work pushes us

to be more creative. Second, BDQ and rifapentine remains a combination of interest, and there may be ways to exploit the strengths of both agents together. Third, we should never underestimate the importance of the controls. We have to mix daring, imagination, and caution in the right balance. This work by this leading group helps us greatly. ∎

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