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Novel Regimens Identified in Mice for Treatment of Latent Tuberculosis Infection in Contacts of Patients with Multidrug-Resistant Tuberculosis

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Preventing the development of tuberculosis (TB) in contacts of patients with multidrug-resistant TB (MDR-TB) by the treatment of latent TB infection (LTBI) is highly desirable. However, few safe, well tolerated, and effective drugs are available to treat MDR-LTBI and the published guidance is limited. Fortunately, six new chemical entities from four classes developed to treat TB have entered clinical trials in the past decade. We tested three of these drugs alone and in combination in an experimental paucibacillary LTBI chemotherapy model using BALB/c and C3HeB/FeJ mice immunized with a recombinant strain of *Mycobacterium bovis* bacillus Calmette-Guérin (rBCG30) and then challenged with a low-dose aerosol of *M. tuberculosis* H37Rv. The regimens tested contained bedaquiline (TMC), PA-824 (Pa), sutezolid (PNU), and/or one of two fluoroquinolones. Control mice received rifampin (RIF) or isoniazid (INH). In BALB/c mice, TMC-containing regimens and the Pa-PNU combination were the most active test regimens and were at least as effective as RIF. Pa, PNU, and levofloxacin had activity comparable to that of INH. Virtually identical results were observed in C3HeB/FeJ mice. This study confirms the potent activity of TMC observed previously in BALB/c mice and highlights Pa alone or in combination with either PNU or a fluoroquinolone as a regimen worthy of evaluation in future clinical trials of MDR-LTBI. Given their closer pathological representation of human TB lesions, C3HeB/FeJ mice may become a preferred model for the experimental chemotherapy of LTBI. Future studies should evaluate additional clinically relevant LTBI regimens in this strain including relapse as an endpoint.

In 2012, *Mycobacterium tuberculosis* was responsible for an estimated 1.3 million deaths and 8.6 million incident cases of active tuberculosis (TB), including 450,000 cases of multidrug-resistant TB (MDR-TB), as defined by resistance to rifampin (RIF) and isoniazid (INH) (1). Compared to drug-susceptible TB, MDR-TB is associated with lower treatment success rates and higher mortality rates, independently of HIV status (1, 2). Resistance to additional drugs is associated with even worse outcomes (3). The prevalence and incidence of active TB among contacts of MDR-TB patients have been estimated at 3% and 165 per 10,000 person-years, respectively (4). Thus, treatment of latent TB infection (LTBI) among close contacts of MDR-TB patients (MDR-LTBI) to prevent the development of active MDR-TB is highly desirable. However, few data exist to support the choice of a treatment regimen or its duration (5–7). New drugs in clinical development may offer additional treatment options for MDR-LTBI. For example, bedaquiline (TMC) recently received accelerated approval from the U.S. Food and Drug Administration for the treatment of MDR-TB. Other new agents in clinical trials include the nitroimidazole derivative PA-824 (Pa) and the oxazolidinone sutezolid (PNU; previously known as PNU-100480), each of which has demonstrated sterilizing activity in animal models of TB in addition to promising evidence of efficacy against active TB in early phase II clinical trials (8–14).

To better understand the potential of these three new drugs (TMC, Pa, and PNU) in the treatment of MDR-LTBI, we evaluated their efficacy, both alone and in combination, in an established model of LTBI chemotherapy in BALB/c mice that accurately ranks the potency of existing LTBI regimens in a manner that is consistent with their clinical use and, at least for rifamycin-based regimens, cures mice that receive the recommended treatment durations (15, 16). TMC has already demonstrated efficacy comparable to that of RIF in this model (16). Two fluoroquinolones, levofloxacin (LFX) and moxifloxacin (MFX), were included because they are commonly recommended for the treatment of MDR-LTBI. MFX alone was less effective than INH in an earlier iteration of this model, but the combination of MFX with Pa was more active than INH (11). Although MFX is more potent than LFX against *M. tuberculosis*, LFX may have a lower propensity to prolong the corrected QT (QTc) interval and may therefore be safer to use in combination with TMC and other agents which also prolong the QTc interval (17, 18).

Murine models of LTBI are often criticized because mice are not thought to develop LTBI and commonly used mouse strains do not develop necrotic granulomas, where latent tubercle bacilli are thought to reside in humans (19–21). However, the clinicopathological features of the small subset of humans with LTBI at highest risk of developing active TB (i.e., those most likely to benefit from the treatment of LTBI) remain unclear. Mice with stable paucibacillary infection after *M. bovis*

Received 6 December 2013 **Returned for modification** 26 December 2013
Accepted 30 January 2014
Published ahead of print 3 February 2014
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Supplemental material for this article may be found at http://dx.doi.org/10.1128/AAC.02658-13.

doi:10.1128/AAC.02658-13

TABLE 1 Lung CFU counts of BALB/c mice

Regimen or parameter	Strain, mean lung CFU count[a] (log_{10}/lung) ± SD (no. of mice) at:				
	Wk −12	Wk −6	Day 0	Wk 4	Wk 8
Untreated	rBCG30, 2.51 ± 0.13 (4)	rBCG30, 4.87 ± 0.24; H37Rv, 1.04 ± 0.23 (4)	rBCG30, 3.18 ± 0.55; H37Rv, 4.23 ± 0.05 (4)	rBCG30, 3.32 ± 0.43; H37Rv, 3.89 ± 0.69 (4)	rBCG30, 3.47 ± 0.49; H37Rv, 4.30 ± 0.31 (4)
INH				2.62 ± 0.76 (4)	2.49 ± 0.27 (4)
RIF				3.33 ± 0.22 (4)	1.04 ± 0.36 (4)
LFX				4.01 ± 0.28 (4)	3.11 ± 0.31 (4)
MFX				3.60 ± 0.47 (2)	3.18 ± 0.16 (4)
TMC				1.87 ± 0.41 (4)	0.89 ± 0.26 (4)
Pa				3.45 ± 0.36 (4)	2.56 ± 0.28 (4)
PNU				3.33 ± 0.22 (4)	2.59 ± 0.52 (4)
TMC-LFX				2.02 ± 0.21 (4)	0.91 ± 0.37 (4)
TMC-Pa				2.37 ± 0.25 (4)	1.28 ± 0.14 (4)
TMC-PNU				2.36 ± 0.19 (4)	0.80 ± 0.19 (4)
Pa-LFX				3.33 ± 0.20 (4)	1.88 ± 0.41 (4)
Pa-PNU				2.31 ± 0.65 (4)	1.08 ± 0.39 (4)
PNU-LFX				3.72 ± 0.28 (4)	2.58 ± 0.09 (4)
TMC-Pa-PNU				1.01 ± 0.33 (4)	0.00 ± 0.00 (4)
Total	4	4	4	58	60

[a] Week −12 corresponds to the day of aerosol immunization, week −6 corresponds to the day of *M. tuberculosis* challenge, and day 0 corresponds to the start of treatment. The no. of mice is the number initially allocated to each treatment arm; *n* is the number of mice contributing to the mean CFU counts (if *n* is not provided, *n* = the no. of mice initially allocated). CFU counts of rBCG30 were determined from hygromycin-containing plates, and CFU counts of H37Rv were determined from TCH-containing plates. All CFU counts are taken from TCH-containing plates unless otherwise indicated.

bacillus Calmette-Guérin (BCG) immunization may provide an efficient model for experimental chemotherapy of LTBI, as the efficacy of clinically relevant regimens is well represented (15, 16). The fidelity of this murine model for LTBI chemotherapy may be further enhanced if stable paucibacillary infection occurs in the context of necrotic granulomas, which have recently been described in C3HeB/FeJ mice (20, 22–25). Thus, we nested an experiment to determine whether stable paucibacillary infection could be produced in C3HeB/FeJ mice and to compare the efficacy of a subset of novel drug regimens in both BALB/c and C3HeB/FeJ mice.

MATERIALS AND METHODS

Mycobacterial strains. A recombinant BCG strain overexpressing the 30-kDa major secretory protein and possessing a hygromycin resistance marker (rBCG30) was mouse passaged, frozen in aliquots, and then subcultured before infection in Middlebrook 7H9 broth (containing 10% OADC [oleic acid-albumin-dextrose-catalase]; Fisher, Pittsburgh, PA) with 0.1% Tween 80 (Sigma-Aldrich, St. Louis, MO). *M. tuberculosis* H37Rv was prepared as a frozen stock with a known titer and then thawed and diluted in 7H9 broth before infection, as previously described (26).

Antimicrobials. INH, RIF, MFX, LFX, TMC, Pa, and PNU were obtained and formulated for oral administration as previously described (10, 18).

Aerosol BCG immunization and infection with *M. tuberculosis*. All animal procedures were approved by the Animal Care and Use Committee of Johns Hopkins University. Female BALB/c (Charles River, Wilmington, MA) and C3HeB/FeJ (Jackson, Bar Harbor, ME) mice 5 to 6 weeks old were immunized via aerosol with an Inhalation Exposure System (Glas-Col, Terre Haute, IN) and a log-phase broth culture of rBCG30 (optical density [OD] at 600 nm, 0.5). Six weeks later, BALB/c and C3HeB/FeJ mice were infected via aerosol with *M. tuberculosis* H37Rv by using 300- and 500-fold dilutions of the frozen stock, respectively. One day after infection, two mice from each of four aerosol runs were humanely killed to determine the number of bacteria implanted in their lungs.

Chemotherapy. The experimental schemes used are detailed in Tables 1 and 2 for each mouse strain. Treatment was initiated 6 weeks after *M. tuberculosis* infection (day 0), following the randomization of mice into each experimental arm. Each treatment was administered by gavage 5 days/week for 2 months (8 weeks). The treatment regimens administered to BALB/c mice were INH, RIF, LFX, MFX, TMC, Pa, PNU, TMC-LFX, TMC-Pa, TMC-PNU, Pa-LFX, Pa-PNU, PNU-LFX, and TMC-Pa-PNU. C3HeB/FeJ mice received the same regimens, with the exception of MFX, Pa-LFX, Pa-PNU, PNU-LFX, and TMC-Pa-PNU. The following drug doses (16, 27, 28) were used for each mouse strain and drug combination: INH, 10 mg/kg; RIF, 10 mg/kg; LFX, 200 mg/kg; MFX, 100 mg/kg; TMC, 25 mg/kg; Pa, 50 mg/kg; PNU, 50 mg/kg.

Assessment of treatment efficacy. Treatment efficacy was assessed on the basis of lung CFU counts after 1 and 2 months of treatment. Quantitative cultures of lung homogenates were performed on selective 7H11 agar plates (Becton, Dickinson, Franklin Lakes, NJ) enriched with 10% OADC (basic agar). Plates containing the same basic agar were supplemented with (i) 4 mg/liter of 2-thiophene carboxylic acid hydrazide (TCH) (Sigma, St. Louis, MO) to select for *M. tuberculosis* or (ii) 40 mg/liter of hygromycin (Roche Diagnostics, Indianapolis, IN) to select for rBCG30, as previously described (16, 29). For the week 4 and week 8 time points, the same agar media were used with or without 0.4% activated charcoal to prevent drug carryover, as previously described (9, 16).

Plates were incubated for up to 60 days at 37°C before final CFU counts were determined. CFU counts reported for rBCG30 and *M. tuberculosis* are the counts determined on hygromycin-containing and TCH-containing plates, respectively.

Susceptibility of rBCG30 to LFX and oxazolidinones. The susceptibilities of H37Rv and rBCG30 to LFX, linezolid (LZD), PNU, and its sulfoxide metabolite PNU-101603 were determined in 7H9 broth. The inoculum was prepared by diluting a log-phase broth culture to an OD of approximately 0.1. Tubes containing a range of 2-fold dilutions of drug were inoculated with 100 μl of this diluted sample and incubated at 37°C. The MIC was defined as the lowest drug concentration that prevented visible growth after 14 days of incubation.

Statistical analysis. CFU counts (x) were log transformed (as $x + 1$) before analysis. Group means were compared by one-way analysis of variance (ANOVA) with Bonferroni's posttest using GraphPad Prism version 5 (GraphPad, San Diego, CA). A P value less than 0.05 was considered significant.

TABLE 2 Lung CFU counts of C3HeB/FeJ mice

Regimen or parameter	Strain, mean lung CFU count[a] (log_{10}/lung) ± SD (no. of mice) at:				
	Wk −12	Wk −6	Day 0	Wk 4	Wk 8
Untreated	rBCG30, 2.56 ± 0.02 (4, $n = 3$)[b]	rBCG30, 5.04 ± 0.19; H37Rv, 0.76 ± 0.16 (4)	rBCG30, 3.88 ± 0.25; H37Rv, 4.32 ± 0.41 (4, $n = 2$)[c]	rBCG30, 2.51 ± 1.42; H37Rv, 4.58 ± 0.57 (5)	rBCG30, 2.62 ± 0.4; H37Rv, 3.78 ± 0.73 (5)
INH				3.53 ± 0.34 (6)	2.87 ± 0.42 (6)
RIF				2.59 ± 0.47 (6)	0.85 ± 0.56 (6)
LFX				3.60 ± 0.66 (6)	3.93 ± 0.50 (6, $n = 5$)[d]
TMC				1.87 ± 0.21 (6)	0.48 ± 0.20 (6)
Pa				3.51 ± 0.65 (6)	2.76 ± 0.32 (6)
PNU				3.47 ± 0.40 (6)	2.60 ± 0.43 (6)
TMC-LFX				1.86 ± 0.36 (6)	0.18 ± 0.28 (6)
TMC-Pa				2.16 ± 0.74 (6)	0.29 ± 0.36 (6)
TMC-PNU				2.09 ± 0.33 (6)	0.72 ± 0.17 (6)
Total	3	4	3	59	58

[a] Week −12 corresponds to the day of aerosol immunization, week −6 corresponds to the day of *M. tuberculosis* challenge, and day 0 corresponds to the start of treatment. The no. of mice is the number initially allocated to each treatment arm; *n* is the number of mice contributing to the mean CFU counts (if *n* is not provided, *n* = the no. of mice initially allocated). CFU counts of rBCG30 were determined from hygromycin-containing plates, and CFU counts of H37Rv were determined from TCH-containing plates. All CFU counts are taken from TCH-containing plates unless otherwise indicated.

[b] One mouse died during the infection procedure.

[c] One mouse died because of cage flooding, and one mouse had no colonies isolated on TCH-containing plates.

[d] The lung homogenate sample was lost when a glass homogenizer broke during the homogenization procedure.

RESULTS

Treatment efficacy in BALB/c mice. Lung CFU counts are presented in Table 1. One day after immunization of BALB/c mice, the mean (standard deviation) CFU count of rBCG30 in their lungs was 2.51 (0.13) log_{10}. Six weeks later (at week −6), this grew to 4.87 (0.24) before decreasing to 3.18 (0.55) by 12 weeks postinfection (day 0) and remaining stable in untreated mice thereafter.

One day after *M. tuberculosis* infection (week −6), the mean CFU count of *M. tuberculosis* in the lungs was 1.04 (0.23) log_{10}. By day 0, 6 weeks later, this grew to 4.23 (0.05). It remained stable in untreated mice thereafter: 3.89 (0.69) at week 4 and 4.30 (0.3) at week 8.

After 1 month of treatment, INH and TMC were the only monotherapy regimens that were significantly more effective than no treatment. The difference between the log CFU counts (Δlog) of the untreated group and the treated groups at week 4 was 2.02 ($P < 0.001$) for TMC and 1.27 ($P < 0.01$) for INH. All TMC-containing combinations were more effective than no treatment but not significantly different from TMC alone, although TMC-Pa-PNU produced the highest Δlog compared to no treatment (2.89, $P < 0.001$). Among the TMC-sparing combinations, only Pa-PNU was more effective than no treatment (Δlog = 1.59, $P < 0.001$).

After 2 months of treatment, all of the regimens tested were more effective than no treatment. TMC and RIF were the most effective monotherapy regimens (Δlog = 3.41 [$P < 0.001$] and 3.26 [$P < 0.001$], respectively). Pa and PNU alone were as effective as INH. The fluoroquinolones had more limited activity (Δlog = 1.12 and 1.19 for MFX and LFX, respectively, compared to no treatment, versus Δlog = 1.82 for INH), but the differences among MFX, LFX, and INH were not statistically significant. TMC-Pa-PNU was again the most effective combination, rendering all five mouse lungs culture negative. The most effective two-drug combinations were the TMC-containing combinations and Pa-PNU (Δlog = 3.22, $P < 0.001$), which had comparable efficacies. Again, no two-drug regimen was more effective than TMC alone. The Pa-LFX combination was associated with a lower CFU count than Pa alone, but this difference was not statistically significant (Δlog = 0.68, $P = 0.057$ [Mann-Whitney test]).

Because the addition of activated charcoal to TCH-containing 7H11 agar compromised the inhibitory effect of TCH, we cannot be certain that colonies counted as *M. tuberculosis* on TCH-charcoal-containing plates were not rBCG30 instead of *M. tuberculosis*. However, the mean lung CFU counts on TCH-charcoal plates were significantly higher than those on hygromycin-charcoal plates for nearly all regimens, indicating that the CFU counts on the former plates were not significantly affected by incomplete suppression of rBCG30 growth. However, this was not the case for mice treated with PNU or LFX alone, where plates containing TCH or hygromycin had similar CFU counts and could have led to the underestimation of the activity of these two regimens. Interestingly, among mice treated with the PNU-LFX combination, CFU counts on TCH-containing plates were significantly higher than those on hygromycin-containing plates.

Treatment efficacy in C3HeB/FeJ mice. Lung CFU counts are presented in Table 2. One day after the immunization of C3HeB/FeJ mice, the mean CFU count of rBCG30 in their lungs was 2.56 (0.02) log_{10}. At week −6, this grew to 5.04 (0.19) before decreasing to 3.88 (0.25) by 12 weeks postinfection (day 0) and remaining stable in untreated mice thereafter, similar to that of BALB/c mice.

One day after *M. tuberculosis* infection (week −6), the mean CFU count of *M. tuberculosis* in the lungs was 0.76 (0.19) log_{10}. By day 0, this grew to 4.32 (0.41). However, this value omits data from one out of three mice which was culture negative for *M. tuberculosis* at this time point, indicating that some C3HeB/FeJ mice did not receive an adequate infectious dose. *M. tuberculosis* CFU counts remained stable in untreated mice thereafter: 4.58 (0.57) at week 4 and 3.78 (0.73) at week 8, similar to those of BALB/c mice.

The treatment results of C3HeB/FeJ mice were very similar to those of BALB/c mice, in terms of both the magnitude of the treatment effect and the efficacy rankings. For example, after 2 months of treatment, TMC and RIF were again the most effective

monotherapy regimens, followed by INH, Pa, and PNU. However, unlike in BALB/c mice, LFX treatment was not significantly more active than no treatment in C3HeB/FeJ mice. No TMC-containing regimen was more effective than TMC alone. Seven mice receiving a TMC-containing regimen were culture negative at 2 months, as was one mouse receiving RIF. The possibility that one or more of these culture-negative mice did not receive an adequate infectious dose of *M. tuberculosis* cannot be excluded. However, these mice also had negative cultures on hygromycin-containing plates (hence, no cultivable BCG). All of the mice receiving non-TMC-containing regimens had detectable colonies on TCH-containing plates (see Table SA1 in the supplemental material), suggesting that the overall proportion of mice without productive *M. tuberculosis* infection was small.

Susceptibility of rBCG30 to LFX and oxazolidinones. The MIC of PNU was 0.5 μg/ml for both H37Rv and rBCG30. The MIC of both its metabolite PNU-101603 and LZD was 2 μg/ml for both strains.

DISCUSSION

This study supports and extends prior efforts to evaluate novel regimens for MDR-LTBI in murine models by confirming the potent activity of TMC, highlighting Pa- and PNU-containing regimens as potential TMC sparing regimens and advancing C3HeB/FeJ mice as a potentially preferable alternative model of stable paucibacillary infection.

This study confirmed prior observations of the potent activity of TMC in a well-established BALB/c mouse model of the chemotherapy of LTBI and extended this observation to C3HeB/FeJ mice. These results indicate that TMC may be an effective short-course regimen for the treatment of LTBI in contacts of MDR-TB patients with efficacy comparable to that of RIF against drug-susceptible infections. No two-drug TMC-containing regimen outperformed TMC alone, but the 3-drug combination of TMC-Pa-PNU was superior.

Although TMC has received accelerated approval for the treatment of active MDR-TB and is currently being evaluated in a phase III clinical trial for this indication (14, 30), safety concerns prompted by a small excess of deaths among patients receiving TMC compared to those receiving a placebo in phase II trials (study TMC207 C208, clinicaltrials.gov NCT00449644, reported in reference 31) have led to a reluctance to study or recommend TMC for otherwise healthy contacts of MDR-TB patients. Our study indicates that regimens based on Pa alone or in combination with either LFX or PNU may represent alternatives for the treatment of MDR-LTBI. For example, the Pa-PNU combination was as effective as any TMC-containing regimen, as well as the RIF control regimen, indicating the potential for a short-course (e.g., 4 months or less) regimen. Pa alone was comparable to INH, and the addition of LFX appeared to improve the regimen's activity, although not to the extent of adding PNU. Importantly, these regimens, if proven safe and effective, may also offer rifamycin-sparing short-course options for persons taking medications that interact with rifamycins, including those living with HIV and receiving protease inhibitor-based antiretroviral therapy. A phase II trial evaluating a combination of Pa with MFX and pyrazinamide for 8 weeks in active-TB patients was recently completed, and plans for a phase III trial are under way. These studies will provide valuable long-term safety data for Pa-containing regimens.

As we have observed in a prior iteration of the present model, fluoroquinolone monotherapy was of limited efficacy (11). If Pa and/or PNU individually are ultimately at least as effective as fluoroquinolones, as suggested by our results, this could limit the long-term use of fluoroquinolones for MDR-LTBI, which may be associated with the selection of resistance in other bacterial pathogens, which could threaten the utility of these highly effective agents against other important infections.

An important aspect of the present study is the recapitulation of our previously validated paucibacillary infection model in C3HeB/FeJ mice. Compared to BALB/c mice, C3HeB/FeJ mice may become the preferred strain to use for this model. In humans with LTBI, infecting bacilli are believed to reside in necrotic granulomas, where specific microenvironmental conditions such as hypoxia may influence their susceptibility to drugs (21). Therefore, it has been assumed that animals that develop such necrotic granulomas are preferred as models of LTBI. Indeed, the granuloma is so characteristic of human infection that its absence has provoked criticism of murine TB models. The evidence presented here, that rBCG30-immunized C3HeB/FeJ mice develop a stable paucibacillary infection in which RIF is more active than INH in a manner consistent with human data demonstrating 4 months of RIF to be effective treatment of LTBI while 6 to 9 months of INH is required, provides important support for the future use of C3HeB/FeJ mice in preclinical efficacy studies of candidate LTBI regimens. Despite responses similar to those obtained with the regimens tested here in BALB/c and C3HeB/FeJ mice, this may not be the case for other drugs in the future. Additional experiments with regimens for which human outcome data exist or will become available, such as RIF-pyrazinamide and rifapentine-INH, and including the evaluation of relapse rates as the gold standard measure of sterilization are needed to fully justify the adoption of this new model. Additional pathology studies are also warranted to characterize the lesions produced during stable paucibacillary infection in this strain.

Our study has several limitations. First, the addition of activated charcoal to 7H11 adsorbed TCH and reduced its effectiveness in suppressing rBCG30 growth. In fact, a *post hoc* analysis revealed that the lowest effective dose of TCH is four times higher (i.e., 16 mg/liter) in agar containing 0.4% charcoal than in plain agar. Second, the low-dose aerosol infection necessary to produce a paucibacillary infection in C3HeB/FeJ mice led to the identification of at least one mouse not receiving a dose sufficient to cause a productive infection as intended at the day 0 time point. As TCH did not completely prevent BCG growth on charcoal plates, we could not confirm *M. tuberculosis* infection in all of our C3HeB/FeJ mice. However, among 13 untreated control mice at the day 0, M1, and M2 time points, this was the only mouse for which the CFU counts on TCH-containing plates (selecting for H37Rv) were not at least 1 log higher than the CFU counts on hygromycin-containing plates (selecting for rBCG30). Thus, we assume that, at most, 5 to 10% of the C3HeB/FeJ mice might not have been infected with *M. tuberculosis*. The absence of significant outliers and similar efficacy rankings of each regimen after 4 and 8 weeks of treatment provide support that any C3HeB/FeJ mice that did not develop a productive infection prior to treatment did not significantly impact the overall conclusions.

In conclusion, this study indicates that stable paucibacillary

infection can be achieved in C3HeB/FeJ mice and that the overall activities of INH and RIF are consistent with their efficacy in humans according to the recommended treatment durations, as previously observed in BALB/c mice (15, 16). However, because of its propensity to develop necrotic granulomas upon infection with *M. tuberculosis*, the former strain may ultimately be preferable as a paucibacillary model for the chemotherapy of LTBI. Additional comparative studies of regimens for which human efficacy data are, or will be, available are warranted to further explore the utility of C3HeB/FeJ mice in this model. As previously observed in BALB/c mice, TMC alone appears to be as effective as RIF against paucibacillary infections in C3HeB/FeJ mice, indicating that it may be an effective drug for the treatment of MDR-LTBI in contacts of MDR-TB patients. In BALB/c mice, the alternative combination of Pa-PNU had additive activity comparable to that of TMC-containing regimens, and Pa-LFX, while not as potent as Pa-PNU, was likely superior to Pa alone. These novel drug regimens warrant consideration for clinical trials evaluating the treatment of latent infection in contacts of patients with MDR-TB.

ACKNOWLEDGMENT

This work was supported by grant OPP1037174 from the Bill and Melinda Gates Foundation.

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