Contribution of Moxifloxacin or Levofloxacin in Second-Line Regimens with or without Continuation of Pyrazinamide in Murine Tuberculosis

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Rationale: High-dose levofloxacin (L) (1,000 mg) was as active as moxifloxacin (M) (400 mg) in an early bactericidal activity trial, suggesting these fluoroquinolones could be used interchangeably. Whether pyrazinamide (Z) contributes sterilizing activity beyond the first 2 months in fluoroquinolone-containing second-line regimens remains unknown.

Objectives: We compared the efficacy of M and high-dose L alone or in combination with ethionamide (Et), amikacin (A), and Z given for 2 or 7 months.

Methods: A pharmacokinetic study was performed to determine the L dose equivalent to 1,000 mg in humans. Treatment started 2 weeks after aerosol infection with *Mycobacterium tuberculosis* H37Rv. Mice received M or L alone or in combination with 2 months of EtZA followed by 5 months of Et or EtZ.

Measurements and Main Results: After 2 months of treatment, lung colony-forming unit (CFU) counts were similar in mice receiving either fluoroquinolone alone, but, after 4 and 5 months, CFU counts were 2 log₁₀ lower in mice receiving M. Mice receiving 2MEtZA/3MEt and 2LEtZA/3LEt had 1.0 and 2.7 log₁₀ lung CFUs, respectively. When Z was given throughout, both regimens rendered mice culture negative by 5 months, and most mice did not relapse after 7 months of treatment, with fewer relapses observed in the M group after 6 and 7 months of treatment.

Conclusions: In murine tuberculosis, M had superior efficacy compared with L despite lower serum drug exposures and may remain the fluoroquinolone of choice for second-line regimens. Z contributed substantial sterilizing activity beyond 2 months in fluoroquinolone-containing second-line regimens, largely compensating for L's weaker activity.

Keywords: moxifloxacin; levofloxacin; MDR-TB; pharmacokinetics; mouse model

As safe, well-tolerated, orally bioavailable agents with bactericidal activity against *Mycobacterium tuberculosis*, fluoroquinolones have become cornerstone drugs for treatment of multidrug-resistant tuberculosis (MDR-TB) (1–5). Among currently marketed fluoroquinolones, moxifloxacin (M) is the most potent

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Optimizing second-line regimens for treating multidrug-resistant tuberculosis may improve outcomes, enable shortening of the treatment duration, and prevent further resistance. Fluoroquinolones are considered cornerstone agents in second-line regimens. Levofloxacin at 1,000 mg daily is as active as moxifloxacin at 400 mg during the first 7 days of treatment, is less expensive, is more widely available, and may be less likely to prolong the QT interval. However, the two drugs have never been compared head-to-head in combination with other drugs in a clinical trial. Pyrazinamide exerts sterilizing activity only during the first 2 months of treatment with the first-line regimen, but the extent and duration of its contribution to second-line regimens is not well studied.

What This Study Adds to the Field

This study shows that, despite seemingly less favorable pharmacodynamics and comparable activity during the initial 2 months of treatment, moxifloxacin contributes greater bactericidal activity to second-line regimens than levofloxacin during the continuation phase of treatment in a murine tuberculosis model. If these results are reproducible in humans, moxifloxacin may be the fluoroquinolone of choice in the treatment of tuberculosis. The clear benefit of extending pyrazinamide administration during the continuation phase of even the most potent second-line regimens in mice suggests this agent may contribute important sterilizing activity beyond the first 2 months in second-line regimens. These findings warrant further study in clinical trials.

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in vitro (6) and has the best pharmacodynamic profile (7). M also showed the greatest activity against rifampin-tolerant *M. tuberculosis in vitro* (8), a model of persistent infection. In murine models, M has proven to be the most potent fluoroquinolone (9, 10). Substitution of M at 100 mg/kg for isoniazid (H) in the first-line regimen of isoniazid, rifampin, pyrazinamide (Z), and ethambutol promotes more rapid cure in mice (11, 12). In humans, M showed early bactericidal activity (EBA) similar to that of H or rifampin (13, 14) and promotes similar or more rapid sputum conversion when substituted for H or ethambutol, respectively, although the magnitude of the effect and the endpoint for which the effect was observed differed among trials (15–18).

M has certain limitations that have pushed clinicians to search for alternative fluoroquinolones. M is more expensive, more likely to prolong the QT interval, more susceptible to metabolic induction by rifamycins, and not available in many settings where MDR-TB is prevalent. Levofloxacin (L) is less potent than M

in vitro but may be used at higher doses without undue risk of toxicity (19). Indeed, L at 300 mg/kg is more active than L at 200 mg/kg in mice (20). In humans, L at 1,000 mg has EBA over 7 days, which is comparable to that of H or M at 400 mg daily (20). Additionally, L is less expensive, less likely to prolong the QT interval, less susceptible to metabolic induction by rifamycins, and more widely available than M. Veziris and colleagues (21) previously found that M at 100 mg/kg was more active than L at 200 mg/kg when combined with ethionamide (Et), Z, and amikacin (A) in mice, but that study did not include higher doses of L matching exposures obtained with 1,000 mg daily in humans and did not include relapse as the gold standard measure for sterilizing activity. Thus, the first objective of this study was to compare the contribution of high-dose L equivalent to the 1,000 mg human dose to that of the standard M dose in an idealized second-line drug regimen (antituberculosis drug regimens devoid of H and rifampin used for MDR-TB) in a murine model of TB.

Pyrazinamide is the only available drug with clear-cut sterilizing activity that is active against some MDR-TB strains. In combination with rifampin and H in the first-line regimen, its contribution is limited to the first 2 months of treatment because administration beyond that point has been shown to have no added value (22, 23). However, there are limited clinical data regarding the contribution of Z to second-line regimens and no data regarding the duration of therapy necessary for maximal effect. A study in mice indicated that Z continued to contribute sterilizing activity beyond the first 2 months when combined with streptomycin and H (24). The second objective of this study was to determine whether Z contributes sterilizing activity when used in combination with a potent fluoroquinolone and an aminoglycoside and, if so, for what duration of treatment.

To pursue the above-mentioned objectives, we evaluated the contributions of M, high-dose L, and Z to second-line combination regimens in a murine TB model similar to that previously used by Veziris and colleagues (21), except that mice were infected by the aerosol rather than intravenous route and outcomes assessed included relapse after discontinuation of treatment.

Portions of this work were presented as posters and reported in the form of abstracts (25, 26).

METHODS

Bacterial Strain

M. tuberculosis H37Rv was passaged in mice and frozen in aliquots at -80°C . After thawing, an aliquot was subcultured in Middlebrook 7H9

broth (Fisher, Pittsburgh, PA) with 10% oleic acid–albumin–dextrose–catalase (Difco, Detroit, MI) and 0.1% Tween 80 (Sigma, St. Louis, MO).

Antimicrobials

M was donated by Bayer (Rolling Meadows, IL). L was donated by Johnson and Johnson (Raritan, NJ). Other drugs were purchased from Sigma. All drugs were prepared in distilled water. Solutions were prepared weekly and stored at 4°C as described previously (27). All drugs were administered by gavage 5 days per week in 0.2 ml by esophageal cannula with the exception of A, which was injected subcutaneously. The dosages of rifampin, H, Z, M, L, Et, and A were 10, 25, 150, 100, 300, 50, and 100 mg/kg of body weight, respectively. Rifampin was given at least 1 hour apart from other drugs to prevent pharmacokinetic antagonism as previously demonstrated (28, 29).

Pharmacokinetics of Levofloxacin

Single-dose pharmacokinetics of L in serum was evaluated in uninfected female BALB/c mice (Charles River, Wilmington, MA) after a 200, 300, or 400 mg/kg oral dose. Groups of three mice were anesthetized with isoflurane and exsanguinated by cardiac puncture at 0.5, 1, 1.5, 2, 4, 6, 8, 10, and 24 hours after dose administration. Serum was harvested and frozen at -80°C before analysis by a validated HPLC method (20). Concentration data were analyzed by standard noncompartmental techniques using WinNonlin (version 5.2.1; Pharsight, Mountain View, CA).

Aerosol Infection

All procedures involving animals were approved by the institutional Animal Care and Use Committee of Johns Hopkins University. Six-week-old female BALB/c mice were used for all experiments. Mice were infected with *M. tuberculosis* H37Rv as previously described (27) in four aerosol runs of 101 mice. Twelve mice (three mice per run) were killed on the day after infection to determine the number of colony-forming units (CFUs) implanted in the lungs. Another 20 mice (five mice per run) were killed on the day of treatment initiation to determine baseline CFU counts. Ten mice went untreated to confirm the virulence of the infecting strain. The remaining mice were randomly distributed into treatment groups (Table 1).

Treatment

The efficacy of M and high-dose L was compared when both drugs were administered alone and in combination with other second-line drugs. Z was administered throughout the treatment or for the first 2 months only to allow us to examine its contribution during the continuation phase. Beginning 13 days after aerosol infection, mice were randomized to receive no treatment (negative controls [group 1]), 2 months of RHZ

TABLE 1. SCHEME OF THE EXPERIMENT

Regimens*	Number of mice used to determine lung CFU counts (number of mice held for relapse after treatment completion) [†]						
	D-13	D0	M2	M4	M5	M6	M7
Control groups							
Infected, untreated	12	20					
2 mo RHZ + RH			5	5	+10 monitored for survival 5 (30)	5 (30)	
Test groups							
M alone			5	5	5		
L alone			5	5	5		
2 mo MEtZA + MEt			5	5	5		
2 mo MEtZA + MEtZ				5	5 (30)	5 (30)	5 (30)
2 mo LEtZA + LEt			5	5	5		
2 mo LEtZA + LEtZ				5	5 (30)	5 (30)	5 (30)

Definition of abbreviations: A = amikacin; CFU = colony-forming unit; Et = ethionamide; H = isoniazid; L = levofloxacin; M = moxifloxacin; R = rifampin; Z = pyrazinamide.

* Drugs were administered orally, 5 d/wk, at the following doses: R at 10 mg/kg, H at 25 mg/kg, Z at 150 mg/kg, M at 100 mg/kg, L at 300 mg/kg, and Et at 50 mg/kg. A was administered subcutaneously at 100 mg/kg. Mice were killed at the following times: 1 d after infection (D-13); 14 d after infection (D0); and after 2, 4, 5, 6, and 7 mo of treatment (M2, M4, M5, M6, and M7, respectively).

[†] Numbers in parentheses indicate that 30 mice were killed 3 mo after completing the indicated duration of treatment to assess for relapse.

followed by 4 months of RH (2RHZ/4RH; positive controls [group 2]), M alone (group 3), L alone (group 4), 2MEtZA/3MEt (group 5), 2MEtZA/3MEtZ (group 6), 2LEtZA/5LEt (group 7), or 2LEtZA/5LEtZ (group 8) (Table 1).

Assessment of Treatment Efficacy

The change in lung CFU counts was assessed after 2, 4, and 5 months of treatment by performing quantitative cultures of lung homogenates on oleic acid–albumin–dextrose–catalase enriched 7H11 agar medium (Difco) as previously described (27, 29).

Treatment was continued in three groups for up to 6 months in the case of group 2 2RHZ/4RH or up to 7 months in the case of group 6 2MEtZA/5MEtZ and group 8 2LEtZA/5LEtZ. Cohorts of 30 mice were held without treatment for 3 months after completing 5, 6, or 7 months of treatment before being killed to assess the relapse rate. Relapse was defined by a positive culture upon plating the entire lung homogenate.

Statistical Analysis

CFU counts were log transformed before analysis. Multiple pairwise comparisons of group means at each time point were made by one-way ANOVA with Bonferroni *post hoc* test. Two-way ANOVA with Bonferroni *post hoc* test was used to determine whether the effects of M and L treatment were affected by duration of treatment. Group proportions were compared using Fisher's exact test and adjusting for multiple comparisons using Bonferroni correction. All analyses were performed with Prism v.4.01 (GraphPad, San Diego, CA).

RESULTS

Pharmacokinetics of L

The single-dose serum pharmacokinetics parameters for L are shown in Table 2 alongside prior results for M obtained using similar methods (30). The increases in peak serum concentration ($C_{\max}$) and area under the serum concentration–time curve from time zero to infinity ($AUC_{0-\infty}$) were less than proportional with increasing dose. Half-life values after the 300 and 400 mg/kg doses were somewhat longer than those after the 200 mg/kg dose, which may indicate longer absorption or other factors. Because the ratio of AUC to minimum inhibitory concentration (AUC/MIC) is believed to be the pharmacodynamic driver of activity for fluoroquinolones against *M. tuberculosis* (31) and other pathogens, 300 mg/kg of L in mice was selected to be equivalent to the 1,000 mg dose in humans, which produces a median $AUC_{0-\infty}$ of 137 $\mu\text{g}\cdot\text{h}/\text{ml}$ (32).

Treatment Efficacy

All untreated mice became moribund and were killed within 28 days of infection. There were 10 deaths among treated mice, including one mouse each from group 5 2MEtZA/3MEt and group 7 2LEtZA/3LEt and two and six mice each from group

TABLE 2. PHARMACOKINETIC PARAMETER VALUES FOR LEVOFLOXACIN AND MOXIFLOXACIN IN MICE AFTER SINGLE-DOSE ORAL ADMINISTRATION AND IN PATIENTS WITH TUBERCULOSIS

Drug	Mice*			Humans†		
	Dose (mg/kg)	$C_{\max}$ ($\mu\text{g}/\text{ml}$)	$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h}/\text{ml}$)	Dose (mg)	$C_{\max}$ ($\mu\text{g}/\text{ml}$)	$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h}/\text{ml}$)
Levofloxacin	200	38.8	107.4			
	300	44.6	142.6	1,000	11.6	137
	400	48.5	148.9			
Moxifloxacin	100	14.2	23.6	400	5.9	58

Definition of abbreviations: $C_{\max}$ = peak serum concentration; $AUC_{0-\infty}$ = area under the serum concentration–time curve from time zero to infinity.

* Mean values from present study (levofloxacin) and from Reference 30 (moxifloxacin).

† Median values from Reference 32.

Figure 1. Activity of levofloxacin at 300 mg/kg (5 L₃₀₀) or moxifloxacin at 100 mg/kg (5 M₁₀₀), each administered for 5 months, in comparison to a standard multidrug regimen consisting of 2 months of rifampin, isoniazid, and pyrazinamide followed by 3 months of rifampin and isoniazid (2RHZ+3RH).

6 2MEtZA/5MEtZ and group 7 2LEtZA/5LEtZ, respectively. All deaths happened within the first week of treatment and appeared to be related to gavage and injection. No death was observed in mice receiving L or M alone or 2RHZ/3RH.

The day after aerosol infection, the mean lung log₁₀ CFU count was 4.48 (SD, 0.11). Two weeks after infection, at initiation of treatment, the mean lung log₁₀ CFU count was 7.64 (SD, 0.33) (Figure 1). After 2 months of treatment, mice receiving L and M alone had 5.64 (SD, 0.20) and 5.26 (SD, 0.08) log₁₀ CFU, respectively, in the lungs. The ≥ 2 log₁₀ reduction in CFU from Day 0 indicates the bactericidal activity of these fluoroquinolones. Mice receiving RHZ had 2.95 (SD, 0.07) log₁₀ CFU in the lungs, compared with 3.20 (SD, 0.07) and 3.11 (SD, 0.18) log₁₀ CFU among mice receiving LEtZA and MEtZA, respectively (Figure 2). Whether the fluoroquinolones were administered alone or in combination with EtZA, there were no significant differences in the activity of regimens containing L or M at 2 months. Furthermore, the activity of the LEtZA and MEtZA combinations was not significantly different from that of RHZ.

Mean lung log₁₀ CFU counts among mice receiving L and M alone were 4.62 (SD, 0.12) and 3.17 (SD, 0.33), respectively, after 4 months of treatment ($P < 0.001$) and 4.52 (SD, 0.13) and 2.61 (SD, 0.45), respectively, after 5 months ($P < 0.001$) (Figure 1). The difference in lung CFU counts between the two treated groups increased significantly over time ($P < 0.001$). After 4 and 5 months of treatment, mice receiving 2RHZ/RH were culture negative, with the exception of one mouse with 3 CFUs at 4 months. When Z was omitted from the continuation phase, both fluoroquinolone-containing second-line regimens were inferior to 2RHZ/3RH on the basis of lung CFU counts after 4 and 5 months ($P < 0.001$) (Figure 2). Among mice receiving 2LEtZA/LEt and 2MEtZA/MEt, mean lung log₁₀ CFU counts were 2.91 (SD, 0.25) and 1.89 (SD, 0.21) after 4 months and 2.27 (SD, 0.23) and 1.00 (SD, 0.15) after 5 months, respectively. These differences were statistically significant at both time points and increased over time ($P < 0.001$), indicating that, in combination with Et during the continuation phase, M has greater bactericidal activity than L. Taken together with the results with either fluoroquinolone alone, these findings indicate that L at 300 mg/kg and M at 100 mg/kg have similar bactericidal activity over the first 2 months of treatment but that M has significantly greater activity against persisting organisms thereafter. However, even the combination of M and Et was not as active as rifampin and H. Administration of Z in the continuation phase increased activity of both the

Figure 2. Activity of second-line regimens containing high-dose levofloxacin (L) or moxifloxacin (M), with or without pyrazinamide (Z), in combination with ethionamide (Et) and amikacin (A), in comparison to the first-line regimen (2RHZ+3RH).

fluoroquinolone-containing second-line regimens at 4 and 5 months ($P < 0.001$) and improved the activity of the L-containing regimen such that it was no longer inferior to the M-containing regimen. Both second-line regimens rendered all mice culture negative after 5 months of treatment, an effect indistinguishable from that of 2RHZ/3RH. However, the mean lung CFU count among mice receiving 2LEtZA/2LEtZ was higher than that among mice receiving 2RHZ/2RH ($P < 0.001$).

Relapse results after treatment for 5, 6, or 7 months are shown in Table 3. Among mice treated with 2RHZ/RH, 23 and 0% relapsed after 5 and 6 months of treatment, respectively. Higher relapse rates were observed in mice treated with 2MEtZA/MEtZ and 2LEtZA/LEtZ after 5 and 6 months ($P < 0.0005$), although the results after 7 months of treatment with these second-line regimens were comparable to those observed with 5 months of the first-line regimen, further highlighting the sterilizing activity of Z. The M-containing regimen resulted in lower relapse rates than the L-containing regimen after 6 and 7 months of treatment. These differences were not statistically significant when analyzed by time point by Fisher's exact test ($P = 0.16$ at 6 and 7 mo). However, when mice treated for 6 or 7 months were combined, the proportion of mice with relapse was significantly lower in the M arm than in the L arm ($P = 0.04$).

DISCUSSION

The two main findings of this study are that high-dose L was less efficacious than M and that Z contributed sterilizing activity well beyond the first 2 months of treatment in the idealized second-line regimen tested in this murine model of TB. A recent EBA study showed that L at 1,000 mg daily has an EBA similar to a 400 mg daily dose of M or gatifloxacin (20), raising hopes that this less expensive and more widely available fluoroquinolone that is less likely to prolong the QT interval and less vulnerable to metabolic induction by rifamycins may substitute for M, the more potent fluoroquinolone *in vitro*. This expectation is in line with the comparable AUC/MIC and C_{max} /MIC values achieved with high-dose L and M (20). However, the present study suggests that matching the two fluoroquinolones on these parameters does not assure similar sterilizing activity. Despite producing AUC/MIC and C_{max} /MIC values greater than those observed with M at 100 mg/kg/d (30, 31), L at 300 mg/kg/d was less efficacious than M when used alone or in combination with second-line drugs, especially after the first 2 months of treatment.

The basis for the superior overall efficacy of M over L after comparable initial bactericidal activity in this murine model is

TABLE 3. RELAPSE* AFTER TREATMENT COMPLETION

Regimen	% (Proportion) of Mice Relapsing after Treatment for:		
	5 mo	6 mo	7 mo
2 mo RHZ + RH	23 (7/30)	0 (0/30)	Not done
2 mo MEtZA + MEtZ	97 (28/29)	59 (17/29)	20 (6/30)
2 mo LEtZA + LEtZ	100 (26/26)	79 (23/29)	38 (11/29)

Definition of abbreviations: A = amikacin; Et = ethionamide; H = isoniazid; L = levofloxacin; M = moxifloxacin; R = rifampin; Z = pyrazinamide.

*Relapse was defined by a positive culture upon plating the entire lung homogenate harvested 3 mo after completing the indicated duration of treatment.

not clear. Two *in vitro* studies have suggested that M may be more active than L against persistent *M. tuberculosis*. Hu and colleagues found M to be more potent than L than predicted by MIC alone in two *in vitro* models of bacterial persistence (8). Furthermore, Malik and colleagues found that M may be unique among marketed fluoroquinolones in its ability to kill *M. tuberculosis* in the presence of the protein synthesis inhibitor chloramphenicol (33, 34). Improved drug delivery to the site of infection may be an additional reason for the greater potency of M. M concentrates inside macrophages and neutrophils to a greater extent than L (35, 36). This may lead to higher exposures for M relative to L in our murine model in which *M. tuberculosis* resides almost entirely intracellularly. M has been shown to accumulate preferentially in the cellular cuff of rabbit lung granulomas (37). However, the implications of such preferential intracellular penetration for the comparative sterilizing activity in human TB lesions are unclear because the location of persistent *M. tuberculosis* remains to be determined. Whether our results are relevant to treatment of pre-XDR and XDR-TB with fluoroquinolone resistance is uncertain. Several clinical studies have suggested that M still lends activity when resistance to ofloxacin has been demonstrated (38, 39), likely because achievable M concentrations at the site of infection still exceed the MIC. However, immunomodulatory effects of fluoroquinolones may also play a role (40, 41).

The second main finding that Z contributed sterilizing activity throughout the length of treatment with the second-line regimens is evident when comparing the efficacy of 2MEtZA/3MEt and 2LEtZA/3LEt with that of 2MEtZA/3MEtZ and 2LEtZA/3LEtZ, respectively. In each case, the continuation of Z was the key determinant of lung culture conversion within 5 months. Indeed, the use of Z throughout largely abrogated the difference observed between MEt and LEt continuation phase regimens. The sterilizing activity of Z under acidic conditions *in vitro*, in mice, and in humans is well documented (22, 42). Indeed, the addition of Z to regimens containing rifampin and H permits shortening the duration of TB treatment from 9 to 6 months and constitutes one basis of modern short-course TB therapy (22, 23). However, continuation of Z beyond the first 2 months of treatment with combinations containing rifampin and H does not further shorten the duration of treatment in mice or in humans, whereas continuation of Z beyond the first 2 months of the second-line regimen studied here shortened the duration of treatment necessary to render lung cultures negative. Whether longer courses of Z in this or other second-line regimens in mice will reduce the treatment duration required to prevent relapse requires further experimentation. The reason(s) Z does not contribute sterilizing activity to the first-line regimen when administered beyond the first 2 months is unclear but may be related to overlapping sterilizing effects of Z and rifamycins against some persistent bacilli and/or possibly antagonistic effects of H (12, 24, 29, 43). Alongside recent clinical observations, our results support current WHO recommendations to include Z alongside later-generation

fluoroquinolones throughout the first 8 months of treatment with second-line regimens and highlight the important role that reliable Z susceptibility testing could play in determining the optimum duration of treatment (44, 45). If the clinical situation mirrors our results in mice, susceptibility of the infecting isolate to Z may indicate the potential for short-course therapy of 9 months or less if Z is continued. On the other hand, continuing Z in the face of resistance may not provide any treatment-shortening benefit while increasing the risk of intolerance and/or toxicity, as observed with fluoroquinolone-Z combinations used to treat latent TB infection among MDR-TB contacts (46–49). Given the favorable interactions between Z and new TB drugs in development and rising concerns over Z resistance among MDR-TB isolates, improved susceptibility testing methods for Z, including genotypic resistance testing, will continue to require attention in the future (50–53).

Our study has several limitations. It is based on an experimental murine model that does not recapitulate all aspects of human TB. The contribution of Z and the relative potency of M and L may be inordinately influenced by the predominantly intracellular nature of infection in mice. To date, however, murine models have provided an accurate representation of the contribution of Z to existing TB regimens (24) and the comparative EBA of H, M, and L (3, 9, 20). However, results in this model have not always been confirmed in clinical trials using sputum culture conversion as a surrogate endpoint (17, 54) for cure. Second, it may be argued that the more rapid clearance of the fluoroquinolones in mice than in humans results in different serum pharmacokinetic profiles that make extrapolation of the results to humans difficult. However, we evaluated drug doses that matched the median AUC/MIC for L and biased the achieved AUC/MIC and C_{max}/MIC values (which correlate best with fluoroquinolone activity in experimental models) in favor of L in this comparative study (31).

In conclusion, our results indicate that M has greater bactericidal activity and may contribute greater sterilizing activity than high-dose L during the continuation phase of treatment in this murine model of TB. If this finding is confirmed in longer relapse-based mouse experiments evaluating fluoroquinolone-containing second-line regimens that lack other sterilizing agents such as Z or in clinical trials, M may be the preferred fluoroquinolone for second-line TB treatment. A trial comparing the efficacy of these two potent fluoroquinolones in the context of MDR-TB treatment is warranted. Inclusion of Z, when it is active against the infecting isolate, is expected to add important sterilizing activity and may compensate for differences in the fluoroquinolone component.

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

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