

Isoniazid or Moxifloxacin in Rifapentine-based Regimens for Experimental Tuberculosis?

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Rationale: Recent studies have demonstrated that combined substitutions of rifapentine for rifampin and moxifloxacin for isoniazid in the standard, daily, short-course regimen of rifampin, isoniazid, and pyrazinamide produces stable cure in 12 weeks or less. This study was designed to more precisely evaluate the contribution of moxifloxacin and isoniazid to rifapentine-based regimens.

Objectives: We compared bactericidal activity and treatment-shortening potential between regimens consisting of isoniazid or moxifloxacin plus rifapentine and pyrazinamide administered either thrice-weekly or daily.

Methods: Using a mouse model of tuberculosis, we assessed bactericidal activity by performing quantitative cultures of lung homogenates over the first 12 weeks of treatment. Relapse rates were assessed after completing 8, 10, and 12 weeks of treatment to determine the duration of treatment necessary for stable cure.

Measurements and Main Results: After 4 weeks of treatment, daily and thrice-weekly therapy with rifapentine, moxifloxacin, and pyrazinamide was significantly more active than treatment with rifapentine, isoniazid, and pyrazinamide. By 8 weeks of treatment, all mice receiving the moxifloxacin-containing regimens were lung culture negative, whereas those mice receiving the isoniazid-containing regimens continued to be lung culture positive. However, the duration of treatment necessary to achieve stable cure was 10 weeks for daily regimens and 12 weeks for thrice-weekly regimens, regardless of whether isoniazid or moxifloxacin was used. All mice receiving standard daily therapy with rifampin, isoniazid, and pyrazinamide relapsed after 12 weeks of treatment.

Conclusions: These results suggest that regimens consisting of isoniazid or moxifloxacin plus rifapentine and pyrazinamide may dramatically shorten the duration of treatment needed to cure human tuberculosis.

Keywords: tuberculosis; rifapentine; treatment

Treatment of tuberculosis (TB) with the standard, 6-month, short-course regimen of rifampin (R), isoniazid (H), and pyrazinamide (Z) is highly effective in curing drug-susceptible pulmonary TB (1). However, because the regimen is lengthy and complicated, improper provision of treatment and poor adherence are serious obstacles to effective control of TB (2, 3). New treatment regimens that radically shorten the duration of effective therapy are expected to improve treatment success rates and thereby play an important role in controlling the TB epidemic (4).

A recent experiment in the murine model demonstrated that increasing rifamycin drug exposure by replacing R with rifapentine (P) as well as replacing H with moxifloxacin (M) in the standard daily (5 out of 7 days [5/7]) regimen shortened the duration of treatment necessary to prevent relapse from 6 months

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Recent evidence from murine models of tuberculosis suggests that treatment regimens consisting of moxifloxacin, rifapentine and pyrazinamide may halve the length of therapy needed to cure tuberculosis.

What This Study Adds to the Field

This study demonstrates that regimens including rifapentine and pyrazinamide may dramatically shorten tuberculosis therapy whether they are combined with isoniazid or moxifloxacin.

to 3 months or less (5). Furthermore, decreasing the rhythm of drug administration from 5 days per week to 3 days per week did not significantly alter the efficacy of the PMZ regimen, provided that the dose of P was increased accordingly (5).

A second experiment examined the individual contributions of P and M to the overall activity of the daily PMZ regimen. Over the first 4 weeks of treatment, PMZ was more active than PHZ and RMZ, which were, in turn, more active than RHZ. By the 6-week time point, however, PHZ was more active than RMZ. Finally, the proportions of mice relapsing were not significantly different after treatment for 10 weeks with PMZ (0 of 15 [0%]) and PHZ (2 of 15 [13%]), but higher for mice treated with RMZ (8 of 15 [53%]). Hence, despite the clear benefit of replacing H with M in combinations containing a rifamycin and Z in the murine model (5–9), it was the individual replacement of R with P that contributed the greatest treatment-shortening potential to the PMZ regimen (5). This finding suggests that novel regimens based solely on replacing R with P have significant treatment-shortening potential, and could serve as highly effective alternatives to regimens based on replacing both R with P and H with M.

To directly address the respective contributions of H and M to P-based regimens, the current study was designed to fully characterize the differences in bactericidal activity (as determined by serial lung colony-forming unit [cfu] counts) and treatment-shortening potential (as determined by relapse rates after decreasing durations of treatment) between regimens consisting of PHZ and PMZ administered either daily (5/7) or thrice-weekly (3/7) in the murine model. Due to the lack of clinical data on the safety and tolerability of daily and thrice-weekly administration of P, we evaluated a range of doses that are under consideration for human trials.

METHODS

Antimicrobials

Drugs were obtained and stock solutions prepared as previously described (5).

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TABLE 1. SCHEME OF EXPERIMENT

Regimens*	No. of Mice Killed								
	D -13	D 0	Wk 4	Wk 8	Wk 10	Wk 12	Wk 8 (+3)	Wk 10 (+3) [†]	Wk 12 (+3)
Control animals									
(1) Infected, untreated	12	12							
(2) 8 wk R ₁₀ HZ + R ₁₀ H (5/7)			5	5	5	5			15
(3) 8 wk R ₁₀ HZ + R ₁₀ H (3/7)			5	5	5	5			
Treatment groups									
Daily									
(4) 8 wk P _{7.5} HZ + P _{7.5} H (5/7)			5	5	5	5		15	15
(5) 8 wk P ₁₀ HZ + P ₁₀ H (5/7)			5	5	5		15	15	15
(6) 8 wk P ₁₀ MZ + P ₁₀ M (5/7)			5	5			15	15	
Thrice-weekly									
(7) 8 wk P ₁₀ HZ + P ₁₀ H (3/7)			5	5	5	5		15	15
(8) 8 wk P ₁₅ HZ + P ₁₅ H (3/7)			5	5	5			15	15
(9) 8 wk P ₂₀ HZ + P ₂₀ H (3/7)			5	5	5			15	15
(10) 8 wk P ₁₅ MZ + P ₁₅ M (3/7)			5	5	5			15	15

Definition of abbreviations: H = isoniazid; M = moxifloxacin; P = rifapentine; R = rifampin; Z = pyrazinamide.

* Drugs were given orally at the following doses: H, 25 and 50 mg/kg when administered daily (5 out of 7 days [5/7]) and thrice-weekly (3/7), respectively; R, 10 mg/kg; Z, 150 and 225 mg/kg when administered 5/7 and 3/7, respectively; M, 100 mg/kg; P, 10, 15, and 20 mg/kg, as indicated.

[†] Months 8 (+3), 10 (+3), and 12 (+3) indicate that mice were killed 3 months after completing 8, 10, and 12 months of treatment.

Aerosol Infection

Six-week-old female BALB/c mice (Charles River, Wilmington, MA) were aerosol infected with *Mycobacterium tuberculosis* H37Rv using the Middlebrook Inhalation Exposure System (Glas-Col, Terre Haute, IN) with a log-phase broth culture. Mice were infected in four consecutive runs. All animal procedures were approved by the Johns Hopkins University Animal Care and Use Committee.

Chemotherapy

Treatment began 14 days after infection. Drugs were administered by gavage either 5/7 or 3/7 at the following doses: H, 25 and 50 mg/kg when administered 5/7 and 3/7, respectively; M, 100 mg/kg; Z, 150 and 225 mg/kg when administered 5/7 and 3/7, respectively; R, 10 mg/kg; and P, 7.5, 10, 15, and 20 mg/kg (P_{7.5}, P₁₀, P₁₅, and P₂₀, respectively), as indicated.

At the start of treatment (Day 0 [D0]), mice were block randomized by infection run into 10 groups (Table 1). Negative-control mice went

untreated (group 1) and positive-control mice received standard therapy with 2 months of RHZ followed by 1 month of RH 5/7 (group 2) or 3/7 (group 3). To assess the impact of substituting P for R in the standard 5/7 regimen, mice in groups 4 and 5 received 2 months of PHZ followed by 1 month of PH, with P_{7.5} and P₁₀, respectively. To assess the impact of substituting P for R and M for H in the standard 5/7 regimen, mice in group 6 received 2 months of P₁₀MZ followed by 2 weeks of P₁₀M. In order to assess the impact of substituting P for R in the standard 3/7 regimen, mice in groups 7, 8, and 9 received 2 months of PHZ followed by 1 month of PH with P₁₀, P₁₅, and P₂₀, respectively. Finally, to assess the impact of substituting P for R and M for H in the standard 3/7 regimen, mice in group 10 received 2 months of P₁₅MZ followed by 1 month of P₁₅M.

Assessment of Treatment Efficacy

Treatment efficacy was assessed on the bases of lung cfu counts and the proportion of mice with culture-positive relapse after treatment

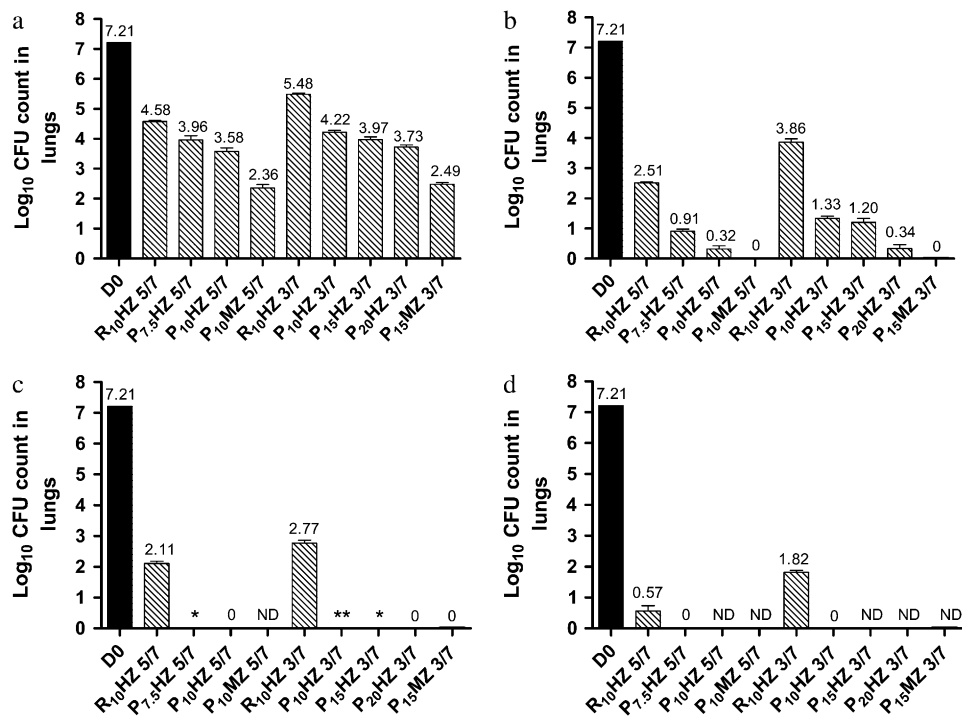


Figure 1. Lung log₁₀ colony-forming unit (CFU) counts at treatment initiation (Day 0 [D0; black bars]) and after (a) 4 weeks, (b) 8 weeks, (c) 10 weeks, and (d) 12 weeks in *Mycobacterium tuberculosis*-infected mice. Data are presented as means and SD (n = 5 mice per time point). H = isoniazid; M = moxifloxacin; ND = not determined; P = rifapentine; R = rifampin; Z = pyrazinamide. *One of five mice harbored 1 cfu/lung; **three of five mice harbored 1 cfu/lung.

completion. Untreated mice were killed the day after infection and 14 days later (D0), at the initiation of treatment. Treated mice were killed for quantitative culture of lung homogenates after completing 4, 8, 10, and 12 weeks of treatment, as previously described (5). The proportion of mice with relapse was assessed by killing a group of mice ($n = 15$ per group) 3 months after completion of treatment. Culture-positive relapse was defined by isolation of 1 cfu or more after plating the entire lung homogenate.

Statistical Analysis

Cfu counts were \log_{10} transformed before statistical analysis. Mean cfu counts were compared using one-way analysis of variance followed by Dunnett's multiple comparison test (GraphPad Prism; GraphPad Software, Inc., La Jolla, CA). The proportions of mice relapsing after completing treatment were compared using Fisher's exact test (STATA 8.2; Stata Corporation, College Station, TX). The type I error rate for multiple comparisons was adjusted by Bonferroni's procedure.

RESULTS

Lung Colony-Forming Unit Counts before Treatment

The day after infection (D -13) the mean lung \log_{10} cfu count (\pm SEM) was 3.66 ± 0.04 . By the initiation of treatment on D0, the mean cfu counts had increased to 7.29 ± 0.09 , 7.13 ± 0.08 , 7.27 ± 0.05 and 7.13 ± 0.04 ($P = 0.26$) in mice infected during infection runs 1, 2, 3, and 4, respectively. All infected, untreated mice ($n = 5$) were killed when they became moribund at 3 weeks after infection.

Lung Colony-Forming Unit Counts during Treatment

After 4 weeks of treatment, all 5/7 P-based regimens had significantly greater bactericidal activity than R₁₀HZ 5/7 ($P < 0.001$) (Figure 1a). Mice treated with P_{7.5}HZ, P₁₀HZ, and P₁₀MZ 5/7 had mean lung cfu counts that were 0.62, 1.00, and 2.22 \log_{10} cfu lower than those of mice treated with R₁₀HZ 5/7, respectively ($P < 0.01$). Likewise, all 3/7 P-based regimens were significantly more active than R₁₀HZ 3/7 ($P < 0.0001$). Mice treated with P₁₀HZ, P₁₅HZ, P₂₀HZ, and P₁₅MZ 3/7 had mean lung cfu counts that were 1.26, 1.51, 1.75, and 2.99 \log_{10} lower than those of mice treated with R₁₀HZ 3/7, respectively ($P < 0.01$).

After 8 weeks of treatment, the greater bactericidal activity of P-based regimens was even more apparent (Figure 1b). Mice that received R₁₀HZ 5/7 harbored 2.51 \log_{10} cfu per lung, whereas those that received P_{7.5}HZ and P₁₀HZ 5/7 harbored 0.91 and 0.32 \log_{10} cfu, respectively ($P < 0.001$), and all five mice treated with P₁₀MZ 5/7 had negative cultures. Mice that received R₁₀HZ 3/7 had more than 3.5 \log_{10} cfu per lung, whereas those that received P₁₀HZ, P₁₅HZ, and P₂₀HZ 3/7 had 1.33, 1.20, and 0.34 \log_{10} cfu per lung, respectively ($P < 0.001$), and all mice treated with P₁₅MZ 3/7 had negative cultures. Therefore, in the standard daily or thrice-weekly regimen of R₁₀HZ, the replacement of R with P resulted in a significant increase in bactericidal activity. Further increases in activity were observed with the additional replacement of H with M.

After 10 weeks of treatment, all mice that received P-containing regimens had negative lung cultures, with the exception of one mouse each in the P_{7.5}HZ 5/7 and P₁₅HZ 3/7 groups, and three mice in the P₁₀HZ 3/7 group (Figure 1c). Each of the five culture-positive mice harbored only 1 cfu in the entire lung. In contrast, mice that received R₁₀HZ 5/7 or 3/7 had more than 2 \log_{10} cfu per lung.

Finally, after 12 weeks of treatment, all mice that received P_{7.5}HZ 5/7 and P₁₀HZ 3/7 were culture negative, whereas mice

TABLE 2. RELAPSE AFTER COMPLETING TREATMENT

Treatment Group*	No. of Mice Relapsing after Treatment % (Proportion)		
	8 wk	10 wk	12 wk
Daily			
R ₁₀ HZ 5/7	—	—	100 (15/15)
P _{7.5} HZ 5/7	—	60 (9/15)	0 (0/15)
P ₁₀ HZ 5/7	67 (10/15)	0 (0/15)	0 (0/15)
P ₁₀ MZ 5/7	27 (4/15)	0 (0/15)	—
Thrice-weekly			
R ₁₀ HZ 3/7	—	—	—
P ₁₀ HZ 3/7	—	87 (13/15)	33 (5/15)
P ₁₅ HZ 3/7	—	53 (8/15)	0 (0/15)
P ₂₀ HZ 3/7	—	7 (1/15)	0 (0/15)
P ₁₅ MZ 3/7	—	7 (1/15)	0 (0/15)

See Table 1 for definition of abbreviations.

* Z administered for the first 2 months of therapy only.

that received R₁₀HZ 5/7 and 3/7 still harbored 0.57 and 1.82 \log_{10} cfu per lung, respectively (Figure 1d).

Culture Status 3 Months after Treatment Completion

Among mice that received 8 weeks of treatment with P₁₀HZ and P₁₀MZ 5/7, relapse occurred in 10 of 15 (67%) and 4 of 15 (27%), respectively (Table 2) ($P = 0.07$). After 2 additional weeks of treatment, no mouse treated with P₁₀HZ or P₁₀MZ 5/7 relapsed. However, 9 of 15 (60%) mice that received the lower P_{7.5} relapsed ($P = 0.0007$, compared with P₁₀HZ and P₁₀MZ). The 12-week treatment with P_{7.5}HZ 5/7 prevented relapse in all mice. As expected, all mice that received R₁₀HZ 5/7 for 12 weeks were culture positive after 3 months of follow-up ($P < 0.0001$, compared with 12 wk of P_{7.5}HZ and P₁₀HZ [5/7]).

Among mice treated with 3/7 P-containing regimens, a similar dose-dependent effect of P on relapse was observed (Table 2). After 10 weeks of treatment with P₁₀HZ, P₁₅HZ, and P₂₀HZ 3/7, relapse was observed in 13 of 15 (87%), 8 of 15 (53%), and 1 of 15 (7%) mice, respectively. When M was substituted for H in the P₁₅HZ regimen, the proportion of mice with relapse fell to 1 of 15 (7%) ($P = 0.014$), indicating the additional benefit of replacing H with M. The 12-week treatment with thrice-weekly P-containing regimens prevented relapse in all mice, except in 5 of 15 (33%) mice treated with P₁₀HZ ($P = 0.04$).

DISCUSSION

The present experiment was designed to determine the differences in bactericidal activity and treatment-shortening potential between PHZ- and PMZ-based regimens in the murine model of TB. Our results demonstrate that daily administration of P₁₀HZ or P₁₀MZ resulted in stable cure of all mice after only 10 weeks of treatment, and that thrice-weekly administration of P₁₅HZ or P₁₅MZ was able to achieve stable cure of all mice after only 12 weeks of treatment. These results reaffirm those of previous studies demonstrating the dramatic treatment-shortening potential of daily and thrice-weekly PMZ regimens (5), and extend those results by demonstrating that similar PHZ regimens may also be capable of shortening the duration of treatment to 12 weeks or less.

Although treatment with either PHZ or PMZ yielded stable cure by 10–12 weeks, treatment with PMZ clearly displayed superior bactericidal activity during the first month of treatment, in which the rates of decline in bacterial colony-forming unit counts were 0.91 and 1.21 \log_{10} cfu/week for P₁₀HZ 5/7 and

P₁₀MZ 5/7, and 0.81 and 1.18 for P₁₅HZ 3/7 and P₁₅MZ 3/7, respectively. The benefit of substituting M for H remained evident after 8 weeks of treatment. All mice that received P₁₀MZ 5/7 or P₁₅MZ 3/7 had negative lung cultures, whereas those mice that received P₁₀HZ 5/7 and P₁₅HZ 3/7 had positive lung cultures. The beneficial impact of substituting M for H has previously been demonstrated in the murine model with both RHZ- and PHZ-based regimens (5, 7, 8). In these studies, the enhanced initial bactericidal activity of M over H after 8 weeks of treatment has ranged from 0.72 log₁₀ cfu/lung for twice-weekly RMZ to 2.46 log₁₀ cfu/lung for daily RMZ; similar results have been observed in studies replacing H with sparfloxacin (10). These findings, along with those presented here, clearly demonstrate that replacing H with M, in either the standard RHZ regimen or the experimental PHZ regimen, significantly increases initial bactericidal activity. Previous studies in the murine model demonstrate that H antagonizes the activity of regimens composed of RZ with and without a fluoroquinolone, and that removal of this antagonistic effect explains much of the beneficial impact of replacing H with M (7, 10, 11). Although the precise mechanism of this effect has not been described, it is unlikely to result from an adverse pharmacokinetic interaction (6). Whether this same antagonistic effect is observed in PZ-based regimens remains unknown, and is currently under investigation. Finally, it is reasonable to question the relevance of this apparent antagonism to the treatment of humans. Thus far, no human trial has been designed to address this issue, although an ongoing clinical trial comparing RHZE, RHZM, and RMZE may help to indirectly address whether this phenomenon is observed in humans.

The finding that both PHZ and PMZ regimens achieved stable cure by 10–12 weeks underscores that the overall treatment-shortening effect is largely driven by the greater sterilizing activity of P over R at the doses studied. This was clearly evident in comparing the results of 12 weeks of treatment with RHZ and P₁₀HZ 5/7. All mice receiving RHZ remained culture positive at the completion of treatment, while all mice receiving PHZ were cured. This dramatic increase in sterilizing activity that occurs upon replacing R with P is likely due to the greater rifamycin drug exposure obtained with P (5, 8, 12). When comparing P to R at the same dose and dosing frequency in the murine model, P produces a superior pharmacodynamic profile, in which the free drug area under the concentration–time curve divided by the minimum inhibitory concentration is 2.5-fold higher, and P concentrations exceed the minimum inhibitory concentration for the entire dosing interval, as compared with 60% of the time for R (5). Overall, these findings suggest that regimens based solely on substituting P for R in the standard RHZ 5/7 or 3/7 regimens may prove, clinically, to be as effective in shortening the duration of therapy as regimens based on substituting both P for R and M for H.

Given the exposure-dependent activity of the rifamycins (13), we hypothesized that increasing the dose of P would result in enhanced sterilizing activity, and thereby decrease the proportion of mice relapsing after treatment. In mice treated with PHZ 3/7 for 10 weeks, increasing the dose from P₁₀ to P₂₀ decreased the occurrence of relapse in a dose-dependent fashion, from 87% with P₁₀HZ to 7% with P₂₀HZ. Likewise, increasing the dose from P_{7.5} to P₁₀ in the PHZ 5/7 regimen reduced the proportion of mice relapsing after 10 weeks of treatment from 60 to 0%. Given that the P doses tested in the current experiment correspond to the same doses in humans, as measured by serum concentration-versus-time profiles, it is reasonable to speculate that increasing P doses in humans would also result in enhanced sterilizing activity (5, 8). Before addressing this hypothesis, however, it will be critical to

establish the safety and tolerability profile of thrice-weekly and daily P.

That thrice-weekly treatment with P₁₅HZ displayed a similar degree of bactericidal and sterilizing activity as treatment with daily P_{7.5}HZ underscores the notion that intermittent regimens can be as active as daily regimens, as long as the P dose is increased accordingly. It is important to stress that this dosing strategy may only be applicable to regimens based on P, as previous clinical studies have reported a strong association between a potentially fatal hypersensitivity syndrome and increasing R doses in intermittent regimens (14). Therefore, P may have a dually beneficial role in the treatment of TB by simultaneously decreasing the duration of treatment and decreasing the frequency of administration without compromising efficacy. These results are especially encouraging, given that a recent systematic review of published clinical trials on RHZ-based regimens reported that decreasing the frequency of administration from daily to thrice weekly or twice weekly increases the risk of relapse (15).

In conclusion, we have used a well-established murine model to determine the treatment-shortening potential of regimens based on PHZ and PMZ. Our study demonstrates that both H- and M-containing regimens produce stable cure in a similar time frame, despite the greater initial bactericidal activity of the PMZ regimen. Therefore, replacing R with P may prove to be a simple alternative to replacing both R with P and H with M in shortening the duration of effective therapy. If daily and thrice-weekly P is shown to be safe and tolerable in humans, P-based regimens may have enormous potential to significantly shorten the treatment of TB.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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