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Effectiveness of Once-Weekly Rifapentine and Moxifloxacin Regimens against *Mycobacterium tuberculosis* in Mice

NACER LOUNIS,[1]* ABDELHALIM BENTOUCHA,[1] CHANTAL TRUFFOT-PERNOT,[1] BAOHONG JI,[1] RICHARD J. O'BRIEN,[2] ANDREW VERNON,[2] GIORGIO ROSCIGNO,[3] AND JACQUES GROSSET[1]

Laboratoire de Bactériologie, Faculté de Médecine Pitié-Salpêtrière, Paris 75634, France[1]; Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia 30333[2]; and Global Alliance for TB Drug Development, New York, New York 10038[3]

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Mice infected with 1.6×10^7 CFU of *Mycobacterium tuberculosis* were treated 14 days later for 6 months with a regimen of once-weekly 10 mg of rifapentine and 75 mg of isoniazid per kg of body weight supplemented with either 150 mg of streptomycin per kg or 100 mg of moxifloxacin per kg during either both the 2-week daily initial and once-weekly continuation phases or only in the daily 2-week initial phase. On completion of treatment, all lung cultures were negative, except for three mice, each with a single colony: two whose rifapentine-isoniazid regimen was supplemented with streptomycin during the whole course of therapy and one whose rifapentine-isoniazid regimen had no initial daily phase, but was supplemented with streptomycin and moxifloxacin during the whole course of therapy. After 3 months of follow-up, positive lung cultures were obtained from 61 and 56% of mice supplemented with streptomycin during either the full course of therapy or only the daily 2-week initial phase, respectively, and 15 and 50% of mice supplemented with moxifloxacin during either the full course of therapy or only the daily 2-week initial phase, respectively. These results suggest that moxifloxacin has sterilizing activity against *M. tuberculosis*.

The operational requirements for the World Health Organization's directly observed treatment (DOT) short-course strategy for the control of tuberculosis (19–21) are difficult to satisfy, particularly in areas in which the health infrastructure is poor and accessibility of services is limited. The requirement posing the greatest challenge is that ingestion of medication actually be observed by a health care provider, i.e., DOT. If the frequency of drug administration could be reduced to once weekly while the efficacy of treatment was maintained, the implementation of DOT would be easier.

Treatment regimens that are based on rifapentine, a drug recently approved by the U.S. Food and Drug Administration for the treatment of pulmonary tuberculosis (11), offer this possibility. The pharmacokinetic parameters of rifapentine are very favorable, because its peak level in serum and half-life are significantly greater than those of other available rifamycin derivatives (7). Good bactericidal and sterilizing activities were observed in mice treated intermittently with 10 mg of rifapentine per kg of body weight at a frequency of once a week (2, 7). The addition of 75 mg of isoniazid per kg of body weight, also given once a week, enhanced the activity of rifapentine in both immunocompetent (normal) and immunodeficient (nude) mice (2), suggesting that the combination rifapentine-isoniazid given once weekly might be an effective intermittent regimen for both the preventive and curative therapy of tuberculosis.

In another study of mice treated for 8 weeks with various once-weekly rifapentine-containing drug regimens, a strong bactericidal effect was consistently observed (5). However the effect was approximately 1 $\log_{10}$ less than that of the standard daily regimen (i.e., rifampin plus isoniazid plus pyrazinamide). With an initial 2-week daily supplement of streptomycin, isoniazid, and pyrazinamide and with the addition of streptomycin to the once-weekly rifapentine-isoniazid combination, the deficit in bactericidal effect of the once-weekly rifapentine-isoniazid regimen was entirely overcome. A subsequent study in mice evaluated various once-weekly rifapentine-isoniazid-containing regimens with and without streptomycin given for 8 months (3). That study showed that 8-month once-weekly rifapentine-isoniazid regimens were successful only when supplemented with an initial 2-month daily isoniazid-rifampin-pyrazinamide phase. When the initial daily phase was reduced to 2 weeks, 8-month, once-weekly regimens containing rifapentine-isoniazid were successful only if supplemented with streptomycin during all phases or with daily isoniazid during the once-weekly phase. This finding was further supported by results of human clinical trials, in which 6-month regimens with a continuation phase of once-weekly rifapentine-isoniazid were modestly less effective than standard twice- or thrice-weekly rifampin-based therapy (17; Tuberculosis Trial Consortium, submitted for publication).

Of the recently developed fluoroquinolones, moxifloxacin has demonstrated potent bactericidal activity against *Mycobacterium tuberculosis* in the mouse model (8, 13), and its long half-life (16) compared to that of isoniazid, suggests that it might be a better pharmacokinetic match with rifapentine. The objective of the present mouse experiment was to determine if moxifloxacin would increase the bactericidal and sterilizing properties of once-weekly rifapentine-isoniazid when substituted for streptomycin during both the daily initial and once-weekly continuation phases of therapy. The efficacy of the regimens was assessed on the basis of their ability to sterilize lung cultures on completion of the 6-month therapy, to prevent the selection of drug-resistant organisms, and to prevent re-

* Corresponding author. Mailing address: Laboratoire de Bactériologie-Hygiène, Faculté de Médecine Pitié-Salpêtrière, 91 Boulevard de l'Hôpital, 75634 Paris, Cedex 13, France. Phone: (33) 1 40 77 97 46. Fax: (33) 1 45 82 75 77. E-mail: lounis@chups.jussieu.fr.

TABLE 1. Experimental design in this study

Treatment group[a]	Total no. of mice	No. of mice sacrificed at[b]:				
		D−13	D0	2 wk	6 mo	9 mo
Control						
A: infected, untreated	50[c]	10	30	10		
B: 6 mo P 1/7	10				10	
C: 2 mo HRZ 5/7 + 4 mo HR 5/7	60			20	20	20
Test						
D: 2 wk HRZS 5/7 + 5.5 mo HPS 1/7	60			20	20	20
E: 2 wk HRZS 5/7 + 5.5 mo HP 1/7	40				20	20
F: 2 wk HRZM 5/7 + 5.5 mo HPM 1/7	60			20	20	20
G: 2 wk HRZM 5/7 + 5.5 mo HP 1/7	40				20	20
H: 6 mo SHPM 1/7	60			20	20	20

[a] The drugs were given at the following dosages in milligrams per kilogram of body weight: rifampin (R), 10; isoniazid (H), 25 and 75 when given, respectively, five times weekly (5/7) and once weekly (1/7); pyrazinamide (Z), 150 (5/7); streptomycin (S), 150; and moxifloxacin(M), 100. Rifapentin (P) was given at 10 mg/kg.

[b] Dates are in relation to the initiation of treatment, which began at 14 days after infection (D0).

[c] Including 10 mice that were kept aside from D0 to follow-up the survival rate.

lapse of culture positivity after 3 months of follow-up without therapy.

MATERIALS AND METHODS

Antimicrobial agents. Rifapentine, rifampin, and pyrazinamide were kindly provided by Hoechst Marion Roussel (Romainville, France), and isoniazid was provided by Laphal (Allauch, France). Streptomycin was purchased from Solvay Pharma (Suresnes, France), and moxifloxacin was a gift from Bayer (Puteaux, France).

***M. tuberculosis* strain.** The H37Rv strain of *M. tuberculosis* was grown on Löwenstein-Jensen medium. Colonies were subcultured in Dubos broth (Diagnostics Pasteur, Paris, France) for 7 days at 37°C. The turbidity of the resulting suspension was adjusted with normal saline to match that of a standard 1-mg/ml suspension of *Mycobacterium bovis* BCG and was further diluted with normal saline to obtain a 0.2-mg/ml suspension for mouse inoculation. The MICs of the drugs in micrograms per milliliter for the H37Rv strain were as follows: rifampin, 0.25; rifapentine, 0.06; isoniazid, 0.1; streptomycin, 2.0; moxifloxacin, 0.5 on 7H11 agar medium; and pyrazinamide, 10 on Löwenstein-Jensen medium at pH 5.5.

Infection of mice. Three hundred eighty female 4-week-old outbred Swiss mice were purchased from the Janvier Breeding Center (Le Genest Saint-Isle, France). They were intravenously infected in the tail vein with 0.5 ml of a bacterial suspension containing approximately 1.6×10^7 CFU of *M. tuberculosis* H37Rv.

Chemotherapy. Following infection, mice were randomly distributed in three control groups (A to C) and five test groups (D to H) of 40 to 60 mice each, except for group B, which had 10 mice (Table 1). The first two control groups were negative controls: group A contained infected and untreated mice to confirm progressive and fatal tuberculosis infection, and group B contained mice treated with once-weekly rifapentine alone to ensure that monotherapy with rifapentine would select rifampin-resistant mutants. The third control group (C) was a positive control that included mice treated with the standard 6-month regimen, of 2 months of daily (five times a week) isoniazid-rifampin-pyrazinamide followed by 4 months of daily isoniazid-rifampin (21). All five test groups of mice were treated for a total of 6 months. Groups D to G received once-weekly rifapentine plus isoniazid for 5.5 months, supplemented with a 0.5-month initial daily phase of rifampin, isoniazid, and pyrazinamide. In groups D and E, streptomycin was added during either the daily initial plus the once-weekly continuation phases or only the daily initial phase, respectively. In groups F and G, similar to groups D and E, moxifloxacin was substituted for streptomycin. In group H, all four drugs, rifapentine, isoniazid, streptomycin, and moxifloxacin, were given once weekly from the start of treatment.

Drug administration was initiated 2 weeks after infection (D0), and continued for 6 months. Streptomycin was diluted in normal saline and given by subcutaneous injection. All other drugs were suspended at the desired concentration(s) in distilled water containing 0.05% agar and were administered by esophageal gavage either five times weekly or once weekly. The suspensions were prepared weekly and stored at 4°C. The drugs were given at the following dosages in milligrams per kilogram of body weight: rifampin, 10; rifapentine, 10; pyrazinamide, 150; isoniazid, 25 and 75 when given five times weekly and once weekly, respectively; streptomycin, 150; and moxifloxacin, 100 given five times weekly or once weekly. The dosages were the same as those in our previous experiments (2, 5, 7, 9) and were selected to be as equipotent (similar area under the concentration-time curve [AUC]) as possible to the usual doses given to humans (7, 14).

To provide baseline values, groups of 10, 30, and 10 untreated control mice were sacrificed, respectively, on days 1, 14, and 28 after infection (i.e., D −13, D0, and D +14, respectively, in relation to the initiation of treatment). From each treatment group, 20 mice were sacrificed after 2 weeks to assess the contribution of streptomycin and moxifloxacin during the daily initial phase. Similar groups of mice were also sacrificed on completion of the 6-month course of therapy to assess the ability of the different regimens to render the lungs of mice culture negative. Groups of mice were held without treatment for 3 additional months and then sacrificed to measure the rate of relapse to culture positivity.

Assessment of infection and treatment. Assessments of the severity of infection and the effectiveness of treatments were based on survival rate, spleen weights, gross lung lesions (the severity of which were scored from 0 to ++, the latter referring to a lung that was extensively occupied by tubercles), and total CFU counts in the lungs. At D0 and D +14, CFU counts in the lungs were determined by plating serial 10-fold dilutions of homogenized suspensions onto three Löwenstein-Jensen medium slants per dilution. On completion of treatment, the total amount of homogenized suspension from individual lungs was plated without dilution on 15 Löwenstein-Jensen slants. The results of the cultures were recorded after incubation at 37°C for 6 weeks. Testing of susceptibility to rifampin, isoniazid, and streptomycin was performed by the proportion method (1) with any colonies isolated from lung tissue at the end of treatment.

Statistical analysis. Multiple comparisons among pairs of group means were performed by Bonferroni's method (4). Because five test groups were compared, differences were considered significant at the level 0.005: i.e., $0.05/5(5 - 1)/2$.

RESULTS

Survival rate. As expected, after intravenous infection with more than 10^6 CFU of the H37Rv strain, untreated control mice (group A) began to die from day 18 after infection, and all were dead by day 41. The survival rate of group B mice was 100%, indicating that the once-weekly dose of 10 mg of rifapentine per kg alone could effectively prevent deaths caused by infection with *M. tuberculosis*. In all treated groups, the survival rates were 90 to 100% during the first month of treatment. However, some mice died during treatment because of accidents during gavage or injection of streptomycin. Except for one mouse in group H (which died on D0) and three mice each in groups F (which died on D0, D1, and D2) and G (which died on D1, D2, and D2), all deaths (4 in group C, 6 in group D, 6 in group E, 6 in group F, 5 in group G, and 10 in group H) were due to gavage and/or injection accidents and were unrelated to tuberculosis.

Mean spleen weight. The mean spleen weight of infected mice increased more than fourfold during the initial 14 days after infection. After 2 weeks of treatment, the mean spleen weights from mice of groups C, D, F, and H were significantly smaller than that for control mice sacrificed on D0 of treatment. The mean spleen weight of mice supplemented with streptomycin (group D) was the lowest and differed significantly from those of the other groups, except from the rifapentine-isoniazid-streptomycin-moxifloxacin group (Table 2). After 6 months of treatment, the mean spleen weight did not

TABLE 2. Mean spleen weight of mice after 2 weeks and 6 months of treatment and after 3 months of follow-up[a]

Treatment group[b]	Mean spleen wt (mg) ± SD at:		
	2 wk	6 mo	9 mo
B: 6 mo P alone 1/7		307 ± 104	
C: 2 mo HRZ 5/7 + 4 mo HR 5/7	446 ± 94	225 ± 58	264.4 ± 120
D: 2 wk SHRZ 5/7 + 5.5 mo SHP 1/7	356 ± 89	262 ± 132	253.3 ± 48
E: 2 wk SHRZ 5/7 + 5.5 mo HP 1/7		287 ± 51	273.3 ± 93
F: 2 wk MHRZ 5/7 + 5.5 mo MHP 1/7	447 ± 87	269.5 ± 68	236 ± 45
G: 2 wk MHRZ 5/7 + 5.5 mo HP 1/7		240 ± 29	274 ± 62
H: 6 mo SHPM 1/7	414 ± 73	262 ± 63	257 ± 80

[a] Mice were infected intravenously with 1.6×10^7 CFU of *M. tuberculosis* H37Rv. The next day after infection, the mean spleen weight of 10 mice was 127 ± 10 mg, and 14 days after infection (i.e., at onset of treatment), the mean value for 29 mice was 618 ± 113 mg.

[b] H, isoniazid; R, rifampin; Z, pyrazinamide; P, rifapentine; S, streptomycin; M, moxifloxacin; 1/7, once weekly; 5/7, five times weekly.

TABLE 3. CFU counts in mouse lungs after 2 weeks and 6 months of treatment and after 3 months of follow-up without treatment[a]

Treatment group[b]	Log_{10} CFU at 2 wk	% of positive culture at[c]:	
		6 mo	9 mo
B: 6 mo of P alone 1/7		7/10*	
C: 2 mo of HRZ 5/7 + 4 mo of HR 5/7	5.60 ± 0.34	0/20	1/16
D: 2 wk of SHRZ 5/7 + 5.5 mo of SHP 1/7	4.94 ± 0.32**	2/16[d]	11/18
E: 2 wk of SHRZ 5/7 + 5.5 mo of HP 1/7		0/16	10/18
F: 2 wk of MHRZ 5/7 + 5.5 mo of MHP 1/7	5.30 ± 0.45	0/19	2/13
G: 2 wk of MHRZ 5/7 + 5.5 mo of HP 1/7		0/18	7/14
H: 6 mo of SHPM 1/7	5.56 ± 0.25	1/19[d]	7/12

[a] Mice were infected intravenously with 1.6×10^7 CFU of *M. tuberculosis* H37Rv. The next day after infection, the mean CFU count (log_{10}) in the lungs of 10 mice was 5.01 ± 0.17, and at 2 weeks after infection, or the day treatment began, the mean value for 29 mice was 6.46 ± 0.33. A culture was considered positive if any number of colonies was detected. *, five of 7 mice harbored rifampin-resistant mutants; **, significantly different ($P < 0.01$) from groups C, F, and H.

[b] H, isoniazid; R, rifampin; Z, pyrazinamide; P, rifapentine; S, streptomycin; M, moxifloxacin; 1/7, once weekly; 5/7, five times weekly.

[c] Positive cultures yielded highly variable numbers of colonies ranging from one colony to a few hundred colonies.

[d] The positive cultures of lungs yielded a single colony of *M. tuberculosis*, and the organisms from each colony were drug susceptible

differ significantly among the treated groups, except for group E when compared to groups C and G ($P = 0.001$), all of which were significantly smaller than the pretreatment (D0) value. These results indicate that all treatments were equally effective in reversing the splenomegaly caused by tuberculosis infection. At 9 months (i.e., at the end of the 3-month period of follow-up), the mean spleen weights were similar to those at 6 months for all the groups.

Gross lung lesions. At onset of treatment, severe lung lesions (++) were observed in all sacrificed mice of group A. After 2 weeks of treatment (D +14), ++ lesions were still observed in all sacrificed mice of groups C, D, F, and H. However, on completion of 6 months of treatment, ++ lesions were observed only in 5 of 10 mice of group B, apparently due to the emergence of rifampin resistance (described below). After 3 months of follow-up, ++ lesions were observed in only a few mice of groups E (2 of 18), F (1 of 13), G (1 of 14), and H (1 of 12). These results indicate that the lung lesions caused by tuberculosis infection were progressively cured by treatment with all of the combination regimens, but not with rifapentine monotherapy.

Enumeration of CFU in the lungs. The day after intravenous infection, the mean CFU count in the lungs was 5.01 ± 0.17 log_{10}. Two weeks later, it had increased, by about 1.5 log_{10} CFU, to reach 6.46 ± 0.33 log_{10} CFU. After 2 weeks of treatment, all mice were culture positive, and the mean CFU counts in mice in groups C, D, F, and H were significantly smaller ($P < 10^{-5}$) than the pretreatment values (Table 3). The reduction in the CFU counts did not differ significantly between mice in groups C and F and those in groups C and H ($P = 0.025$ and 0.68, respectively). However, the reduction was significantly greater among the mice in group D than among those in groups C and H (0.66 and 0.62 log_{10}; $P = 0.000001$), indicating the strong bactericidal activity of the initial daily supplement of streptomycin. The difference between mice in groups D and F (0.36 log_{10} CFU; $P = 0.006$), suggested that the 100-mg/kg dose of moxifloxacin has somewhat less bactericidal activity than streptomycin.

On completion of the 6-month treatment, 7 of 10 mice in group B that received rifapentine monotherapy were culture positive, with a mean CFU count of 4.19 ± 2.92 log_{10}. Rifampin-resistant strains were isolated in all five mice that had ++ lung lesions. Two mice in group D and one mouse in group H were positive for a single colony. In all other groups of mice, the lung cultures were negative. Consequently, there was no significant difference between all test drug regimens in the rate of culture negativity on completion of the 6-month course of therapy ($P > 0.05$).

After 3 months of follow-up without treatment (i.e., 9 months after initiation of treatment), a positive lung culture was obtained from 1 of the 16 (6%) surviving mice in group C (treated with the standard regimen). Lung cultures were positive from 11 of the 18 surviving mice in group D (61%) and from 10 of the 18 surviving mice in group E (56%). The treatment of these groups had been supplemented with streptomycin either during the full course of therapy (group D) or only the daily 2-week initial phase (group E). The difference in the culture positivity rate was highly significant between groups C and D ($P = 0.0008$) and between groups C and E ($P = 0.002$).

Lung culture was positive in 2 of the 13 surviving mice in group F (15%) and 7 of the 14 mice in group G (50%) whose therapy had been supplemented with moxifloxacin during either the full course of therapy (F) or only the daily 2-week initial phase (G), respectively. The difference in the culture positivity rate between groups F and G ($P = 0.13$) and between groups C and F ($P = 0.85$) was not statistically significant. The difference between groups C and G was statistically significant by conventional criteria, but not when allowance was made for multiple comparisons ($P = 0.02$). Similarly, although moxi-

floxacin had clear sterilizing activity, the difference between groups D and F was significant by conventional criteria, but not by adjusted criteria ($P = 0.01$). Finally, a positive lung culture was obtained from 7 (58%) of 12 surviving mice in group H that fully received once-weekly rifapentine-isoniazid-streptomycin-moxifloxacin treatment.

Prevention of resistance to isoniazid and rifapentine. Colonies isolated on completion of treatment were fully susceptible, indicating that under the experimental conditions presented, all regimens tested were able to prevent the selection of drug-resistant mutants.

DISCUSSION

This experiment was designed to evaluate the possibility that moxifloxacin could replace streptomycin as the key companion drug in a highly effective once-weekly rifapentine-isoniazid combination for the treatment of murine tuberculosis. The experiment demonstrated that the overall antimicrobial activity of moxifloxacin compares favorably with that of streptomycin. When the daily rifampin-isoniazid-pyrazinamide combination was supplemented with moxifloxacin during the initial 2 weeks of therapy, the resulting increase in bactericidal activity was only marginally inferior to the increase resulting from a streptomycin supplement. On the other hand, when moxifloxacin was substituted for streptomycin as a companion drug of the rifapentine-isoniazid combination during the following 5.5 months of once-weekly therapy, the regimen's sterilizing activity was strongly increased. First, all 19 mice treated with moxifloxacin were culture negative on completion of the 6-month therapy, whereas 2 of 16 mice treated with streptomycin were still culture positive (with a single colony). Second, and more importantly, the relapse rates 3 months after treatment were 15% in mice treated with moxifloxacin and 61% in mice treated with streptomycin. The increased sterilizing activity provided by moxifloxacin may be specifically related to the administration of the fluoroquinolone during the 5.5 months of the continuation therapy, because in mice treated with moxifloxacin only during the 2-week daily initial phase, the relapse rate was 50%. In contrast, the relapse rates in mice treated with streptomycin during either the whole course of therapy or the 2-week initial daily phase only were similar: 61 and 55%, respectively. These results are consistent with streptomycin's recognized lack of sterilizing activity against *M. tuberculosis* in mice (6) and in humans (12). They suggest that moxifloxacin has excellent sterilizing activity, even when given only once weekly at the same dose as the daily dose. Such a conclusion is consistent with previous studies of use of fluoroquinolones against *M. tuberculosis* in the murine model (8, 9, 10, 13).

It is of great interest that the efficacy of therapy consisting of 2 weeks of daily rifampin, isoniazid, pyrazinamide, and moxifloxacin followed by a 5.5-month once-weekly treatment with rifapentine, isoniazid, and moxifloxacin was only marginally inferior to that of the 6-month daily standard regimen of 2 months of rifampin, isoniazid, and pyrazinamide followed by 4 months of rifampin and isoniazid. If the antimicrobial activity of the once-weekly regimen could be improved by increasing the once-weekly dose of rifapentine from the standard 10 mg/kg to 15 mg/kg and/or the once-weekly dose of moxifloxacin from 100 mg/kg to 400 mg/kg, such a regimen might be evaluated in clinical trials in patients with pulmonary tuberculosis, because it would be expected to be at least as potent as the standard 6-month daily regimen. Furthermore, recent data on moxifloxacin pharmacokinetics (15, 18) indicate that a dose of 400 mg/kg of body weight in mice would provide an AUC equivalent to that produced by 400 mg per day (7.5 mg/kg of body weight) in humans (16) and therefore that the activity of moxifloxacin in humans might be still greater than the excellent activity we observed in mice treated with 100 mg/kg.

In the present experiment, a full once-weekly drug regimen without an initial daily phase was also tested. Although this regimen contained both streptomycin and moxifloxacin and was able to prevent the emergence of drug-resistant mutants, its antimicrobial activity was not entirely satisfactory. Thus, for the present time, a daily initial phase of at least 2 weeks in duration appears essential in any once-weekly drug regimen.

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