

Efficient Intermittent Rifapentine-Moxifloxacin-Containing Short-Course Regimen for Treatment of Tuberculosis in Mice

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Long-half-life drugs raise the hope of once-a-week administration of antituberculous treatment. In a previous study with the murine model of tuberculosis, the most active intermittent regimen which contained rifapentine (RFP), isoniazid (INH), and moxifloxacin (MXF) given once a week during 5.5 months, preceded by 2 weeks of daily treatment with INH, rifampin (RIF), pyrazinamide (PZA), and MXF, was less active than the standard 6-month daily RIF-INH-PZA regimen. We evaluated with the same model similar regimens in which we increased the dosing of rifapentine from 10 to 15 mg/kg of body weight and of moxifloxacin from 100 to 400 mg/kg. Mice infected intravenously by 6.2×10^6 CFU of *Mycobacterium tuberculosis* H37Rv were treated 2 weeks later when infection was established. After 6 months of treatment, all mice had negative lung culture. After 3 months of follow-up, no relapse occurred in the two groups that received moxifloxacin at 400 mg/kg, whatever the dosage of RFP, and in the group receiving the standard RIF-INH-PZA control regimen. In contrast, in the two groups receiving moxifloxacin at a lower dosage, the relapse rate was significantly higher (13% in mice receiving RFP at 15 mg/kg and 27% in those receiving RFP at 10 mg/kg). Finally, the fully intermittent once-a-week regimen (26 drug ingestions) of INH, RFP (15 mg/kg), and MXF (400 mg/kg) led to a relapse rate of 11%. In conclusion, when used at high dosage, rifapentine and moxifloxacin are very efficient when combined with isoniazid in a once-a-week treatment in mouse tuberculosis.

In order to improve adherence to antituberculous treatment, the World Health Organization (WHO) promotes the use of directly observed therapy, in which the patient ingests each dose of medication under the observation of a health-care provider (18). Due to the duration of treatment, directly observed therapy is difficult to implement in resource-poor countries where health infrastructure is limited. The search for new drugs active against *Mycobacterium tuberculosis* has therefore been directed in three directions: reducing the frequency of administration of antituberculous drugs, reducing the duration of treatment (at present 6 months), and discovering new drugs active against resistant strains.

The discovery of long-half-life antituberculous drugs raises the possibility of once-a-week treatment administration of antituberculous medications that would greatly simplify treatment supervision in resource-poor countries. Rifapentine is a long-acting rifamycin that has shown potent activity against *Mycobacterium tuberculosis* both in vitro and in vivo with the mouse model (4, 7). Rifapentine has been successfully used for human tuberculosis in the continuation phase of treatment, although its use is restricted to human immunodeficiency virus-negative patients who are sputum smear negative at the end of the second month of treatment (1, 2, 23).

With the mouse model of tuberculosis, we demonstrated that even the most active once-a-week combination, i.e., moxi-

floxacin, rifapentine, and isoniazid preceded by a daily administration for 2 weeks, is less sterilizing than the standard WHO 6-month daily regimen (rifampin, isoniazid, and pyrazinamide). In humans, in clinical trials, it has been demonstrated that higher doses of rifapentine can be administered without an increase in toxicity (900 mg instead of 600 mg/day) (3, 14, 25). This information led us to assess the sterilizing activity of regimens containing 15-mg/kg-of-body-weight rifapentine compared to regimens containing 10-mg/kg rifapentine. Moreover, in the previous works, moxifloxacin was used with the mouse model at a lower dose (100 mg/kg) than the equipotent used in humans (27).

In the present study we evaluated the sterilizing activities of intermittent once-a-week regimens containing moxifloxacin (100 or 400 mg/kg) and rifapentine (10 or 15 mg/kg), compared to the standard WHO daily regimen.

MATERIALS AND METHODS

Antimicrobial agents. The compounds were purchased from the following manufacturers: isoniazid (INH) from Laphal (Allauch, France), rifampin (RIF), pyrazinamide (PZA), and rifapentine (RFP) from Aventis (Antony, France), and moxifloxacin (MXF) from Bayer (Puteaux, France).

Infection of mice. The H37Rv strain of *M. tuberculosis* was grown and prepared as described earlier (16). Two hundred forty female 4-week-old outbred Swiss mice, purchased from the Janvier Breeding Center (Le Genest Saint-Isle, France), were inoculated in the tail vein with 0.5 ml of a bacterial suspension containing 6.2×10^6 CFU of *M. tuberculosis* H37Rv.

Chemotherapy. Following infection, mice were randomly allocated to three control groups (1 to 3) and four treatment groups (4 to 7), every treatment group consisting of 10 to 40 mice (Table 1). Group 1 was a negative control group, in which mice were infected but untreated. The mice of group 2 were treated with the standard WHO regimen for drug-susceptible tuberculosis, i.e., 2 months of the combination RIF-INH-PZA, followed by 4 months of RIF-INH. Mice of group 3 were treated with the most active intermittent regimen described so far

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TABLE 1. Once-a-week 6-month treatment of tuberculosis in mice: treatment regimens and experimental design

Treatment group (regimen) ^a	No. of mice	No. of mice sacrificed at:					
		D - 13	D0	2 wk ^a	2 mo ^b	6 mo ^c	9 mo ^d
1 (untreated)	30	10	10				
2 (2 mo RHZ + 4 mo RH 5/7)	40				10	10	20
3 (2 wk RHZM100 5/7 + 5.5 mo P10HM100 1/7)	40			10		10	20
4 (2 wk RHZM400 5/7 + 5.5 mo P10HM400 1/7)	40			10		10	20
5 (2 wk RHZM100 5/7 + 5.5 mo P15HM100 1/7)	30					10	20
6 (2 wk RHZM400 5/7 + 5.5 mo P15HM400 1/7)	30					10	20
7 (6 mo HP15M400 1/7)	30					10	20

^a End of initial 2-week intensive daily phase.

^b End of 2-month initial phase.

^c Completion of treatments.

^d End of 3-month follow-up period.

^e Isoniazid (H), 25 mg/kg daily (5/7) or 75 mg/kg weekly (1/7); rifampin (R), 10 mg/kg daily (5/7); pyrazinamide (Z), 150 mg/kg daily (5/7); moxifloxacin (M), 100 or 400 mg/kg (5/7 or 1/7); rifapentine (P), 10 or 15 mg/kg (1/7).

(16), i.e., 2 weeks of initial intensive daily phase with the combination RIF-INH-PZA-MXF followed by 5.5 months of RFP-INH-MXF given once a week. The mice of groups 4 to 6 were treated daily during the first 2 weeks with the combination RIF-INH-PZA-MXF (initial intensive daily phase) and during the following 5.5 months with the combination RFP-INH-MXF given once a week. Isoniazid was administered at a dosage of 25 mg/kg when given daily and 75 mg/kg when given once a week, rifapentine was given at the dosage of 10 mg/kg in groups 3 and 4 and 15 mg/kg in groups 5 and 6 and moxifloxacin at the dosage of 100 mg/kg in groups 3 and 5 and 400 mg/kg in groups 4 and 6, rifampin was given at a dosage of 10 mg/kg and pyrazinamide at a dosage of 150 mg/kg. Finally, mice of group 7 were treated during 6 months with the combination of INH, RFP (15 mg/kg), and MXF (400 mg/kg) given once a week. The daily regimens were administered as in our previous experiments 5 days a week. All the dosages which are similar to those used in our previous experiments were chosen as equipotent (i.e., similar AUCs) to the usual dosages administered to humans (10, 13, 16).

Treatments were initiated 2 weeks after infection in order to achieve a larger bacterial population. Drug suspensions and gavage were done as described previously (16).

Assessment of infection and treatment. To provide baseline values, 10 untreated mice of group 1 were sacrificed on days 1 and 14 after infection (D-13 and D0 in relation to the initiation of treatment). Serial sacrifices were carried out at fixed intervals for the groups treated with antimicrobial combinations. A parallel group receiving antimicrobial combinations (groups 2 to 7) was held without treatment for three additional months after the end of treatment (follow-up period) and then sacrificed to assess relapses.

The severity of infection and the effectiveness of treatments were assessed by survival rate, spleen weight, gross lung lesion, and numbers of CFU in the lungs (16). CFU counts were determined as previously described (16).

The bactericidal effect of the treatment was defined as a significant decrease of the mean number of CFU in the treated group from the pretreatment value. The sterilizing activity of the treatment was assessed by measuring the percentage of mice with positive lung cultures at the end of the 3-month follow-up period after the completion of therapy.

Statistical analysis. Results were analyzed by the Student *t* test and Fisher's exact probability calculation. Differences were considered significant at the 95% level of confidence.

RESULTS

Survival rate. In untreated control group, group 1, mice began to die at day 35 and all were dead by day 66. No mortality related to tuberculosis was observed in any of the combined treatment groups, a few mice died because of gavage accidents: 4 of 40 in group 2, 5 of 39 in group 3, 7 of 41 in group 4, 4 of 29 in group 5, 8 of 29 in group 6, and 4 of 31 in group 7.

Mean spleen weights. The mean spleen weights increased from 121 ± 16 to 640 ± 131 mg between inoculation (D-13) and the onset of treatment (D0) in the untreated control

group. In all of the treated groups, the spleen weights were significantly lower than the pretreatment value ($P < 0.05$) (data not shown).

Gross lung lesions. Between inoculation (D-13) and the initiation of treatment (D0), the lungs of all mice became extensively occupied by tubercles (++). In the RIF-INH-PZA control group, there were no lung lesions at the end of the 2-month initial phase of treatment except in one mouse which harbored few lesions (+). In groups 3 to 6, at the end of the 2-week initial intensive daily phase of treatment, there were scores of + to ++ for lung lesions in mice receiving MXF at 100 mg/kg and a score of + for lung lesions in those receiving MXF at 400 mg/kg.

After completion of the 6-month treatment, there were no lung lesions in any of the treated mice. At the end of the 3-month follow-up period, no lung lesions reappeared in any of the treated mice.

Enumeration of CFU in the lungs. The bacterial load increased from $4.04 \pm 0.07 \log_{10}$ CFU the day after inoculation (D-13) to $5.57 \pm 0.40 \log_{10}$ CFU at the onset of treatment (D0) (Table 2).

At the end of the 2-week intensive daily phase, the CFU counts were significantly lower than the pretreatment values ($P = 0.001$ for moxifloxacin [100 mg/kg]-containing groups and $P < 10^{-5}$ for moxifloxacin [400 mg/kg]-containing groups) and were slightly but significantly lower for mice treated with moxifloxacin (400 mg/kg) than for those treated with moxifloxacin (100 mg/kg) (3.86 ± 0.27 versus $4.17 \pm 0.18 \log_{10}$ CFU; $P = 0.006$).

At the end of the 2-month initial phase of treatment, the CFU counts in the RIF-INH-PZA control group were significantly lower than the pretreatment values ($1.8 \pm 0.31 \log_{10}$ CFU) ($P < 10^{-5}$).

After completion of the 6-month treatment, all the lungs were culture negative for all the treated mice. At the end of the 3-month follow-up period, there was no relapse either in the RIF-INH-PZA control group or in the two groups which received a 2-week initial intensive daily phase with a combination containing 400 mg/kg moxifloxacin (groups 4 and 6). In control group 3, 4 mice of 15 (27%) relapsed, 2 with a single CFU per lung, 1 with 79 CFU, and the last with >1,000 CFU. In group 5 (same combination as group 3 but with rifapentine given at

TABLE 2. Once-a-week 6-month treatment of tuberculosis in mice: CFU counts in lungs

Group (description) ^a	Lung CFU count (log ₁₀)					Proportion of mice ^b with positive lung culture at 9 mo
	D - 13	D0	2 wk	2 mo	6 mo	
1 (controls)	4.04 ± 0.07	5.57 ± 0.40				
2 (2 mo RHZ + 4 mo RH 5/7)				1.8 ± 0.31	0	0/18 (0)
3 (2 wk RHZM100 5/7 + 5.5 mo P10HM100 1/7)			4.17 ± 0.18		0	4/15 (27)
4 (2 wk RHZM400 5/7 + 5.5 mo P10HM400 1/7)			3.86 ± 0.27		0	0/16 (0)
5 (2 wk RHZM100 5/7 + 5.5 mo P15HM100 1/7)					0	2/16 (13)
6 (2 wk RHZM400 5/7 + 5.5 mo P15HM400 1/7)					0	0/13 (0)
7 (6 mo HP15M400 1/7)					0	2/18 (11)

^a Abbreviations used in this table are the same as those used in Table 1.

^b No. with positive culture / no. studied (%).

15 mg/kg), 2 mice of 16 (13%) relapsed, 1 with 25 CFU and the other with >1,000 CFU. In group 7 (fully intermittent treatment group), 2 mice of 18 (11%) relapsed, 1 with a single CFU and the other with >1,000 CFU.

The relapse rate of the groups treated with 400 mg/kg of moxifloxacin (groups 4 and 6) was significantly lower than that of those treated with 100 mg/kg of moxifloxacin (groups 3 and 5) (0% versus 19%; $P = 0.04$), whereas there was no difference between the groups treated with rifapentine at a dosage of 10 mg/kg (groups 3 and 4) or 15 mg/kg (groups 5 and 6) (13% versus 7%; $P = 0.73$).

DISCUSSION

In the murine model of tuberculosis, the bacilli are mainly intracellular, whereas the majority of bacilli are extracellular in human pulmonary tuberculosis (9, 22). Despite the fact that the murine model of tuberculosis does not precisely mimic human tuberculosis, it has been used for more than 50 years for the development and evaluation of new antituberculous drugs and regimens. With the murine model of tuberculosis, the mice that are apparently sterilized at the end of treatment (i.e., negative cultures of organs) can experience relapse during the following months (19). The follow-up period usually lasts 3 to 6 months (10). For that reason, long-term relapse experiments are of great help in determining the optimal duration of antituberculous drug regimens. In the mouse model, the standard WHO regimen, RIF-INH-PZA, cures mice in 6 months but is followed by a relapse rate of 0 to 10% after 3 to 6 months of follow-up (10, 16, 21). The relapse rate with the RIF-INH-PZA regimen for mice is considered the reference standard that must be reached by any new antituberculous regimen.

With the murine model of tuberculosis, it has been demonstrated that the triple combination of rifapentine, isoniazid, and pyrazinamide given once a week is not able to render mice culture negative after 9 weeks of treatment (15). We conducted a study in which the end point was culture negativity after 6 or 8 months of treatment. All the once-a-week regimens were preceded by a 2-week daily intensive phase of treatment. At the end of antibiotic therapy, the only regimens which led to sterilization of all mice organs were those that associated rifapentine and pyrazinamide combined with either streptomycin once a week or isoniazid once a day. Such regimens are not promising, since streptomycin would require injections and

isoniazid given daily would suppress the benefit of once a week therapy (6).

In the second study, we assessed the contribution of moxifloxacin (100 mg/kg) to the sterilizing activity of once-a-week regimens. The end point was the relapse rate 3 months after the end of antibiotic therapy. The most efficient regimen was the association of moxifloxacin at 100 mg/kg, rifapentine at 10 mg/kg, and isoniazid at 75 mg/kg given once a week and preceded by a 2-week intensive daily phase of rifampin, isoniazid, pyrazinamide, and moxifloxacin (0.5-month RIF-INH-PZA-MXF followed by 5.5-month RFP-INH-MXF). However, this regimen had a higher relapse rate than the standard WHO 6-month daily regimen, although this difference was not significant (relapse rate, 15% versus 6%; $P = 0.85$) (16). A high relapse rate (>50%) was observed with all the other regimens i.e., (i) when moxifloxacin was replaced by streptomycin, (ii) when moxifloxacin was used only in the initial intensive phase of treatment, and (iii) when the 2-week intensive phase was omitted (16).

In the present study, we evaluated the benefit of increasing the dosing of rifapentine, moxifloxacin, or both in intermittent regimens. Indeed, the dosages of these two drugs used in our previous studies somewhat underestimated the dosing used with humans. The area under the concentration-time curve (AUC) of moxifloxacin in the mouse at 100 mg/kg is four times lower than the AUC of moxifloxacin in humans at the usual dosing of 400 mg/day (AUC from 0 to 24 h = 9.5 $\mu\text{g} \cdot \text{h/ml}$ in mouse versus 39 $\mu\text{g} \cdot \text{h/ml}$ in humans) (17, 20, 26). Moreover, the correlation between moxifloxacin AUC and dosing in mice is linear: AUC from 0 to 24 h = 2.2 $\mu\text{g} \cdot \text{h/ml}$ at 25 mg/kg, 4.3 $\mu\text{g} \cdot \text{h/ml}$ at 50 mg/kg, and 9.5 $\mu\text{g} \cdot \text{h/ml}$ at 100 mg/kg (20). Consequently, the 400-mg/kg regimen for the mouse should approximate the AUC obtained for humans at the usual dosing of 400 mg/day.

Rifapentine pharmacokinetic parameters in mice are, as for rifampin, very similar to those observed in humans, and thus, the dosages used with the murine model correspond to those used for humans (5, 13). In our previous studies, we treated mice with rifapentine at 10 mg/kg, which corresponds to 10 mg/kg in humans (600 mg/day). Recent publications demonstrated that higher dosing can be used with humans without increasing toxicity (3, 14, 25), and 900 mg/day seemed to be well tolerated in humans. We evaluated the contribution to the sterilizing activity of rifapentine given at 15 mg/kg.

In the present study, the relapse rate was 0% for the control standard WHO regimen and 27% for the 0.5-month RIF-INH-PZA-MXF regimen, followed by the 5.5-month RFP-INH-MXF control intermittent regimen. These relapse rates compared with those of our previous experiment (16).

The main result of this study was that no relapse occurred with the two intermittent RFP-INH-MXF regimens containing moxifloxacin at 400 mg/kg and preceded by a 2-week intensive daily phase, as observed with the standard RIF-INH-PZA regimen. It is the first demonstration that an intermittent 6-month regimen can achieve a relapse rate as low as that obtained with the standard daily 6-month WHO regimen for murine tuberculosis. Increasing moxifloxacin from 100 to 400 mg/kg significantly reduced the relapse rate. When moxifloxacin was used at the lower dosage (100 mg/kg), an increase in rifapentine dosage (15 versus 10 mg/kg) reduced the relapse rate from 27% to 13%, but this difference was not significant and the regimens did not allow reaching the low level of relapse obtained with the standard WHO 6-month daily treatment.

Until now, the development of an effective intermittent regimen was limited by the lack of a good companion drug for rifapentine. The only bactericidal drug that could be associated with rifapentine was isoniazid. Unfortunately, isoniazid has a short half-life (1 to 3 h in humans), and patients receiving isoniazid-rifapentine once-a-week therapy are indeed treated by rifapentine monotherapy after the clearance of isoniazid and are thus exposed to the risk of failure and selection of rifampin-resistant mutants, as documented in a controlled trial (23, 25). To be effective, an intermittent regimen requires a second long-lasting drug to be associated with rifapentine. Moxifloxacin, which has a relatively long half-life (9 h in humans), seems to be a good candidate. It has proved to be bactericidal against *Mycobacterium tuberculosis*, has sterilizing properties, as demonstrated in vitro and in vivo, and is able to shorten the duration of treatment for both drug-sensitive and drug-resistant tuberculosis (8, 11, 12, 17, 21, 24). The results of the present study further support the interest of moxifloxacin as a companion drug for rifapentine due to its pharmacokinetic characteristics and significant enhancement of the sterilizing activity of rifapentine-containing intermittent drug regimens.

We also investigated the activity of a fully intermittent once-a-week combination of isoniazid, rifapentine (15 mg/kg), and moxifloxacin (400 mg/kg) given during 6 months. Although the sterilizing activity of this regimen was somewhat lower than that of the standard 6-month daily regimen, this difference was not statistically significant, and it is the first time that a fully intermittent regimen has resulted in such a low relapse rate. This rate of relapse, still too high, raises the hope for the development of an effective fully intermittent regimen based on fewer than 30 drug ingestions (26 in the present study).

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