Synergistic activity of R207910 combined with pyrazinamide in murine tuberculosis

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The animal experiment guidelines of the Faculté de Médecine Pitié-Salpêtrière were followed.
ABSTRACT

In previous studies, the diarylquinoline R207910 (TMC207) was demonstrated to have high bactericidal activity when combined with first or second-line antituberculous drugs. Here we extend the evaluation of R207910 in the curative model of murine tuberculosis by assessing the activity of single, double and triple drug associations containing R207910 and isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) or moxifloxacin (MXF) in the setting of a high initial bacillary load (7.3 log10 CFU).

Two months of treatment with the combinations R207910+PZA, R207910+PZA+INH, R207910+PZA+RIF or R207910+PZA+MXF, resulted in culture negative lung homogenates in 70 to 100% of the mice, while mice treated with INH+RIF+PZA (the reference regimen) or RIF+MXF+PZA remained culture positive. Combinations including R207910 but not PZA (e.g. R207910+INH+RIF, R207910+MXF+RIF) were less active than R207910+PZA containing regimens INH+RIF+PZA.

These results reveal a synergistic interaction between R207910 and pyrazinamide. Triple combinations containing these 2 drugs and INH, RIF or MXF have the potential to significantly shorten the treatment duration in patients, provided that these results can be confirmed in long-term experiments including relapses.
INTRODUCTION

Tuberculosis (TB) is the second infectious disease leading to mortality, after AIDS (1, 17). It is estimated that one third of the world’s population is infected with *M. tuberculosis*, 30 million people have active disease, 8 million develop new disease yearly, and 2 to 3 million die annually from tuberculosis (17).

Although the existing standard regimen is very active against tuberculosis, the long treatment duration (6 months), its toxicity and potential for drug-drug interactions particularly in the setting of antiretroviral treatment are all factors underlining the need for new antituberculous drugs. Priorities for tuberculosis drug development are the following: 1) shortening treatment duration, 2) increase compliance by enabling intermittent therapy, 3) identification of drugs with a novel mechanism of action to encertain activity against drug resistant *Mycobacterium tuberculosis*.

Many attempts have been made to discover new antituberculous drugs (2). However, no new agents have been introduced into first line regimen since the discovery of rifampin (13, 15) even though the results of recent trials on moxifloxacin are promising (12).

R207910 (TMC 207) belongs to new family of antituberculosis drugs, the diarylquinolines (1). The compound inhibits the ATP synthase of *Mycobacterium tuberculosis*, a mechanism of action different from that of other antituberculous drugs. Consequently R207910 is active both against sensitive and resistant *Mycobacterium tuberculosis*. When R207910 was combined with standard first line antituberculosis drugs, rifampin, isoniazid and pyrazinamide, it rendered mice culture negative after two months of treatment in the setting of
an initial bacillary load of $6 \log_{10}$. This promising result suggested that combination therapy including R207910 has the potential to reduce the duration of tuberculosis treatment.

We now carried out an experiment with a high initial bacillary load in order to determine more extensively the most promising R207910 containing drug combinations. Double and triple combinations with first-line antituberculous drugs or moxifloxacin were systematically tested. Particular attention was paid to the combination of R207910 and pyrazinamide because our previous data suggested that these might interact synergistically.
MATERIALS AND METHODS

Antimicrobial Agents. R207910 was synthesized by Johnson & Johnson (Beerse, Belgium), while the other compounds were purchased from the following manufactures: isoniazid (INH) from Laphal (Allauch, France), rifampin (RIF), pyrazinamide (PZA) from Aventis (Antony, France) and moxifloxacin (MXF) from Bayer (Puteaux, France).

Infection of Mice. The H37Rv strain of Mycobacterium tuberculosis was grown on Lowenstein-Jensen medium. Colonies were subcultured in Dubos broth (diagnostics Pasteur, Paris, France) for 7 days at 37° C. The turbidity of resulting suspension was adjusted with normal saline to match that of 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. Four hundred and forty female four week old Swiss mice purchased from the Janvier Breeding Center (Le Genest Saint-Isle, France), were intravenously infected in the tail vein with 0.5 ml of bacterial suspension containing approximately 2x10⁶ colony forming units (CFU) of Mycobacterium tuberculosis H37Rv.

Chemotherapy. After two weeks of infection, mice were randomly allocated to 21 groups. A negative control group consisted of 40 mice infected but untreated. Five groups received monotherapy with either rifampin, isoniazid, pyrazinamide, moxifloxacin, or R207910. Eight groups received double drug combinations of the above antibiotics (RIF+INH, RIF+PZA, INH+PZA, RIF+MXF, R207910+RIF, R207910+INH, R207910Z+PZA and R207910+MXF) and seven groups received triple drug combinations (RIF+INH+PZA, RIF+MXF+PZA, R207910+INH+RIF, R207910+MXF+RIF, R207910+INH+PZA, R207910+RIF+PZA and R207910+MXF+PZA).
Treatment was delayed until two weeks after infection to achieve a large and established bacterial population. Compound R207910 was prepared monthly in a hydroxypropyl-β-cyclodextrin solution and kept at 4°C. Other drug suspensions were prepared weekly and kept at 4°C. All drugs were administrated by oral gavage 5 days per week. Rifampin was administered one hour before other drugs to avoid drug-drug interactions (3, 5, 11). The dose of the drugs was selected as to provide areas under the concentration time curve (AUC) in mice that were comparable with those achievable in patients at the usual dosing (11, 14). The following doses were selected: R207910 25mg/kg, rifampin 10mg/kg, pyrazinamide 150mg/kg, moxifloxacin 100mg/kg, isoniazid 25mg/kg. All surviving mice were killed after two months of treatment.

Assessment of infection and treatment. To provide baseline values before initiation of chemotherapy, 10 control mice were killed at day 1 after infection and 20 at day 14 (respectively day−13 and day 0 in relation to the initiation of treatment). In each treatment group, 10 mice were sacrificed after 1 month of treatment and 10 after 2 months of treatment.

The severity of infection and the treatment effect were assessed by survival rate, spleen weight, gross lung lesions (0: no lesions, +: less than 10 tubercles, ++: 10 to 50 tubercles, +++: more than 50 tubercles), and the numbers of colony forming units (CFU) in the lungs. Lungs were aseptically removed and homogenized by a standard procedure (4). Enumeration of CFU was done as previously described (8), but for mice receiving R207910 containing drug combinations, both lungs were harvested and undiluted lung homogenates were cultivated to increase the sensitivity and assess culture negativity more stringently.
Statistical analysis. Mean CFU counts were compared using the Mann-Whitney test. Differences were considered significant at the 95% level of confidence. Proportion of positive mice after 2 months of treatment were compared using the chi-square test.
RESULTS

Survival rate

All untreated mice died between day 20 and day 50. Monotherapy with PZA alone did not completely prevent mortality and seven out of the 20 mice treated with this drug, died of tuberculosis at day 8, 10, 11, 12, 15, 16 and 22 respectively.

Few mice died in the other treated groups: one mouse at day 8 in RIF treated group, 1 mouse at day 1 in INH treated group, 1 mouse at day 5 in RIF+PZA treated group, 3 mice at day 2 and 3 in RIF+MXF treated group, 1 mouse at day 16 in R207910+INH treated group, 2 mice at day 8 and 16 in R207910+MXF treated group, 1 mouse at day 15 in RIF+INH+PZA treated group, 3 mice at day 4, 5 and 19 in R207910+INH+PZA treated group, 1 mouse at day 40 in R207910+MXF+RIF treated group, 1 mouse at day 8 in R207910+MXF+PZA treated group. During the first 10 days of treatment mortality was considered due to tuberculosis as mice harboured +++ lung lesions, had low body weight and important splenomegaly. The five deaths after day 10 were due to gavage accidents.

Mean spleen weights

The mean spleen weight of infected mice increased more than fourfold during the first 2 weeks after infection (from 149 +/-21mg to 524 +/-98mg). One month of treatment with any regimen, except pyrazinamide monotherapy, resulted in a significant decrease of the mean spleen weights from 524 to less than 350 mg. The second month of treatment did not further reduce these spleen weights.
Gross lung lesions.

At the start of treatment, two weeks after the infection, all mice had developed massive (++) gross lung lesions. All treated mice had less severe lesions after one month of therapy. The reduction of lesions was more pronounced in the group receiving R207910 alone, and less pronounced in the group receiving PZA alone, compared to those receiving monotherapy of RIF, INH or MXF. All combinations of 2 or 3 drugs were able to markedly reduce the number of gross lung lesions after one month of therapy.

An additional month of monotherapy with R207910, RIF, INH or MXF further reduced the gross lung lesions but did not cure them completely whereas mice treated with PZA alone developed lung lesions (+++) that were more severe than at the start of treatment. All combinations of drugs were able to further decrease the number of gross lung lesions in comparison with 1 month.

Enumeration of CFU in the lungs.

The mean CFU count in the lungs was 6.0 log10 CFU the day after inoculation and reached 7.2 log10 CFU two weeks later. R207910 alone reduced the CFU count by 3.1 log10 during the first month of treatment and by 5.0 log10 after two months (Table 1). At the end of the 2 months of treatment, the bacillary load was significantly lower in mice treated with R207910 alone compared to mice treated with the other antibiotics (RIF, INH, MXF or PZA, p<0.0025). The activity of R207910 was not increased by adding rifampin, isoniazid or moxifloxacin. In contrast, the addition of PZA significantly enhanced the activity of R207910 as shown in table 2. After only one month of treatment, the CFU
decrease was 5.6 log in mice treated with R207910+PZA versus 3.1 in mice treated with R207910 (p=0.02) and 1.1 log in mice treated with PZA alone. After 2 months of treatment, the CFU count had dropped to undetectable in mice treated with R207910+PZA (-7.2 log) versus 2.3 in mice treated with R207910.

Among the double drug combinations not containing R207910, only RIF+PZA matched the bactericidal activity of R207910 monotherapy after 2 months (Table 2).

Considering the combinations of three drugs, the standard WHO triple combination regimen RIF+INH+PZA reduced the bacillary load by 3.4 log10 after 1 month of treatment and by 5.0 log10 after 2 months. The CFU decrease with RIF+MXF+PZA was 0.7 log less than that with RIF+INH+PZA after 1 month (p=0.0255) but 0.9 log higher than that with RIF+INH+PZA after 2 months (p=0.0042) (Table 3). The addition of RIF, INH or MXF to the double combination R207910+PZA did not increase its bactericidal activity (p>0.05). R207910+MXF+RIF and R207910+INH+RIF were equipotent after 1 and 2 months of treatment (3 log10 reduction of CFU per month) and matched the potency of R207910 monotherapy after one month, but were more active than R207910 after 2 months of treatment (respectively p = 0.037 and p = 0.025).

Importantly, the triple drug combinations containing R207910 but not PZA (R207910+INH+RIF and R207910+MXF+RIF) were less active than the double combination R207910+PZA after 1 (p=0.028 and <0.0036) and 2 months of treatment (p=0.0091 and 0.0009). Finally, all the triple drug combinations containing R207910 and PZA (R207910+INH+PZA, R207910+RIF+PZA and R207910+MXF+PZA) were more active after 1 and 2 months than the two
control regimens RIF+INH+PZA and RIF+MXF+PZA (p < 0.01) but were not more active than the double drug combination R207910+PZA (p>0.05).

At the end of the two months therapy, the percentage of mice with a negative lung culture was 100 for the R207910+PZA group, and ranged between 70 and 78 % for the groups where INH, RIF or MXF was added to R207910+PZA. For all other double or triple drug combinations, the percentage of negative lung cultures varied between 0 and 30%. The percentages of mice with positive lung culture after 2 months of treatment were significantly higher for the 2 control groups (INH+RIF+PZA and MXF+RIF+PZA) than for the R207910+PZA group (respectively p=10-4 and p=10-3). The percentages of positive mice were also significantly higher when R207910 was used without pyrazinamide (R207910+PZA vs R207910+INH+RIF : p=10-3, R207910+PZA vs R207910+MXF+RIF : p=0.0006).
DISCUSSION

In the first study on efficacy of R207910 in mice, the drug combinations R207910+INH+PZA, R207910+RIF+PZA and R207910+INH+RIF+PZA were shown to reduce the bacillary load by approximately 3 log10 per month and were able to render the lung culture negative after 2 months of treatment (1). However, in this first study the initial bacillary load was 6 log10 CFU only and the number of regimens tested was limited. In the present experiment we increased the bacillary load 20-fold and the whole lungs were harvested and tested at the end of treatment in order to be able to evaluate the activity of R207910 in the setting of a high initial bacillary load. The selected doses were chosen in order to obtain pharmacokinetic parameters equipotent to those obtained in man. Since R207910 was not yet tested in tuberculosis infected patients, we used the same dose as in our first experiment i.e. 25 mg/kg 5 days-a-week, a dose which leads to plasma levels in mice equivalent to those reached in human healthy volunteers and which is well tolerated (1).

The present results confirm that monotherapy of R207910 alone is more active than monotherapy with any of the currently available drugs, decreasing the bacillary load by approximately 5 log10 in 2 months versus 3 log10 for rifampin that has the highest activity after R207910. In addition, they confirm that R207910 monotherapy is as active as the standard regimen RIF+INH+PZA.

This new study brings important results on R207910 activity. The most important result is the dramatic activity of the association of R207910 with PZA. Indeed, R207910+PZA reduced the bacillary load by 5.6 after 1 month of treatment, a figure higher by more than 2 log10 than that obtained with the best non R207910 containing drug combination, i.e. RIF+INH+PZA. R207910+PZA was the only drug combination able to render 100% of mice culture negative after 2 months. All the
other R207910 containing double combinations led to only 20 to 30% of culture negative mice. Such level of efficacy has so far only been obtained after 4 months of therapy with the triple drug combination RIF+MXF+PZA (11). Thus, R207910 and PZA clearly act synergistically against Mycobacterium tuberculosis in the murine model. We did not investigate the basis for this synergism in the current study, but DCCD, an aspecific inhibitor of ATP synthase, the enzyme targeted by R207910, has been shown to interact synergistically with pyrazinamide in vitro (19). Pyrazinamide is known to disrupt the membrane potential (19) which is required by ATP synthase to generate ATP. Given that pyrazinamide indirectly inhibits the synthesis of ATP, the synergism of this drug with R207910, specific ATP synthase inhibitor is not surprising. However the level of synergism in vivo is remarkable. There has been concern about the safety of pyrazinamide in humans as number of patients receiving rifampin + pyrazinamide chemoprophylaxis developed severe hepatitis (10). As a consequence there has been attempt in the mouse model to reduce the duration of pyrazinamide (12). The synergism between R207910 and pyrazinamide in the murine model was observed when giving both drugs 5 days a week during 2 months. Due to the toxicity concern of pyrazinamide, the minimum dosing and duration of pyrazinamide required to obtain synergism deserves further specific evaluation. It will be particularly interesting to evaluate synergism in intermittent regimens as the pharmacokinetics of R207910 allow intermittent administration.

Another point assessed in the present study was the interaction of R207910 with the other drugs. Based on our previous results, we were particularly interested in assessing a possible antagonism between R207910 and rifampin (1). Indeed in our previous study, R207910+RIF+PZA seemed to be a little less active than
R207910+INH+PZA after one month of treatment but rendered lung cultures negative after 2 months. In the present study, the double drug combination R207910+RIF reduced the bacillary load by one log10 less than the double drug combination R207910+INH after one month of treatment, however this difference was not statistically significant. After 2 months of treatment the bacillary load was the same in these 2 groups. Thus a significant antagonism between R207910 and rifampin was not confirmed by this study. Based on these results, we can expect that if both R207910 and rifampin were used during the full duration of treatment of tuberculosis, the benefit of adding the powerful sterilizing activity of rifampin to R207910 would exceed a possible small antagonism between these 2 drugs during the very beginning of treatment.

In the present study, the addition of rifampin, isoniazid or moxifloxacin to the R207910+PZA combination could not further increase the activity after 2 months of treatment. In terms of percentage of culture positive mice, adding INH, RIF or MXF to R207910+PZA even seemed to be slightly deleterious although the differences were not statistically significant difference. However, a potential benefit of combining R207910+PZA with a third drug cannot be ruled out for mainly two reasons. First, in a model that assesses sterilizing activity, such as in a long-term relapse experiment in the murine model, R207910+PZA+MXF or RIF may still turn out to be more active than R207910+PZA because of the sterilizing activity of rifampin and moxifloxacin. In a study by Nuermberger and colleagues, RIF+INH+PZA led to culture negativation after 4 months of treatment of mice infected by inhalation, but a further 2 months of treatment were needed to sterilize these mice and prevent relapses after the discontinuation of treatment. In contrast, using the RIF+MXF+PZA combination, the
time required to render the mice culture negative and to prevent the relapse was the same, i.e. 4 months (12). Whether R207910+PZA containing drug combinations will prevent relapses as soon as organ are culture negative (as RIF+MXF+PZA) or will need longer duration of treatment (as RIF+INH+PZA) remains to be determined. The second reason that can justify the addition of a third drug to R207910+PZA is that in man, in contrast to what is observed in the mouse model, pyrazinamide is not able to prevent the selection of resistant mutants to the companion drug (6). Consequently, a double drug combination containing R207910 and PZA could lead to treatment failure due to the selection of R207910 resistant mutants.

The results of the present study also raise the possibility to develop regimens without pyrazinamide or without isoniazid and -pyrazinamide. Although less active than PZA containing regimens, the R207910+RIF+INH or R207910+RIF+MXF drug combinations were at least as active as the 2 control regimens RIF+INH+PZA and RIF+MXF+PZA. This possibility may be attractive because of the risk for severe hepatitis with pyrazinamide and the high rate of resistance to isoniazid in many countries (7, 18).

Finally, our results suggest that it may be possible to develop regimens without isoniazid and rifampin (e.g. R207910+MXF+PZA). Such regimen would be an important alternative to the currently used combination of aminoglycoside, fluoroquinolone, ethionamide and pyrazinamide given for 18 months, as recommended by WHO, to multidrug resistant tuberculosis patients (MDR TB). The most effective regimen without isoniazid and rifampin described so far is the quadruple combination amikacin + ethionamide + moxifloxacin + pyrazinamide, a combination that needs to be given for 9 months to render mice culture negative (16). Interestingly, the bactericidal activity of R207910+MXF+PZA seems equal to
the bactericidal activity of R207910+MXF+PZA+amikacin+ethionamide, a point that opens the way for an effective regimen against MDR TB without injectable agent which would greatly simplify the treatment (9). Moreover, the fully orally administrated R207910+MXF+PZA regimen was in the present study more active than RIF+INH+PZA after two months, raising a hope for a short oral treatment alternative for MDR TB.

In conclusion, the unprecedented activity of the combination of R207910 and pyrazinamide demonstrated in the mouse model opens several possibilities for treating susceptible or multidrug resistant tuberculosis with shorter regimens than those currently recommended by WHO. Further relapse experiments using R207910+PJZA containing regimens associated with rifampin for susceptible tuberculosis or with moxifloxacin and/or ethionamide for multidrug resistant tuberculosis will help to identify the most interesting regimens to be tested in clinical trials.

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REFERENCES


Table 1: Bacterial counts (log10 colony forming units, CFU) in the lungs, after 1 and 2 months of treatment with monotherapy given 5 days / week in murine tuberculosis. Groups were sorted based on efficacy after two months.

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<tr>
<td></td>
<td>D 0</td>
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<tr>
<td>Untreated</td>
<td>7.2 +/-0.5</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>4.1 +/-1.8</td>
<td>2.3 +/-0.7</td>
</tr>
<tr>
<td>R</td>
<td>6.0 +/-0.5</td>
<td>4.1 +/-1.1</td>
</tr>
<tr>
<td>M</td>
<td>5.5 +/-0.5</td>
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</tr>
<tr>
<td>H</td>
<td>4.9 +/-2.1</td>
<td>4.7 +/-0.7</td>
</tr>
<tr>
<td>Z</td>
<td>6.2 +/-0.3</td>
<td>6.4 +/-0.9</td>
</tr>
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J: R207910 (25 mg/kg), R: rifampin (10 mg/kg), M: moxifloxacin (100 mg/kg), H: isoniazid (25 mg/kg), Z: pyrazinamide (150 mg/kg)
Table 2: Bacterial counts (log10 colony forming units, CFU) and proportion of mice with positive culture in the lungs, after 1 and 2 months of treatment with double drug combinations given 5 days / week in murine tuberculosis. Groups were sorted based on efficacy after two months. R207910 monotherapy was added for comparison.

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<td>0.07 +/- 0.2^b</td>
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<td>4.4 +/- 1.1</td>
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<td>RMZ</td>
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</tr>
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^a: 2 mice positive out of 9, one with 2 CFU, the other with 1 CFU.

^b: 3 mice positive out of 10, one with 5 CFU, the 2 other with 1 CFU.

^c: 2 mice positive out of 9, one with 39 CFU, the other with 1 CFU.

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