A randomised Phase II trial to evaluate the toxicity of high-dose rifampicin to treat pulmonary tuberculosis

A. Jindani,* G. Borgulya,* I. Westermann de Patiño,† T. Gonzales,† R. A. de Fernandes,† B. Shrestha,† D. Atwine,§ M. Bonnet,¶ M. Burgos,# F. Dubash,* N. Patel,* A. M. Checkley,* T. S. Harrison,* D. Mitchison,* International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis, St George’s, University of London

*St George’s, University of London, London, UK; †Centros Broncopulmonares, Cruz Roja, Santa Cruz, Bolivia; §German Nepal Tuberculosis Project, Kathmandu, Nepal; ¶Epicentre, Mbarara, Uganda; ‡Epicentre, Paris, France; #Division of Infectious Diseases, School of Medicine, University of New Mexico, Albuquerque, New Mexico, USA

S E T T I N G: Randomised Phase II B clinical trial.

O B J E C T I V E S: To assess whether increasing the dose of rifampicin (RMP) from 10 mg/kg to 15 or 20 mg/kg results in an increase in grade 3 or 4 hepatic adverse events and/or serious adverse events (SAE).

M E T H O D S: Three hundred human immunodeficiency virus negative patients with newly diagnosed microscopy-positive pulmonary tuberculosis (TB) were randomly assigned to one of three regimens: 1) the control regimen (R10), comprising daily ethambutol (EMB), isoniazid (INH), RMP and pyrazinamide for 8 weeks, followed by INH and RMP daily for 18 weeks; 2) Study Regimen 1 (R15), as above, with the RMP dose increased to 15 mg/kg body weight daily for the first 16 weeks; and 3) Study Regimen 2 (R20), as above, with RMP increased to 20 mg/kg. Serum alanine transferase (ALT) levels were measured at regular intervals.

R E S U L T S: There were seven grade 3 increases in ALT levels, 1/100 (1%) among R10 arm patients, 2/100 (2%) in the R15 arm and 4/100 (4%) in the R20 arm (trend test \( P = 0.15 \)). One (R15) patient developed jaundice, requiring treatment modification. There were no grade 4 ALT increases. There was a non-significant increase in culture negativity at 8 weeks with increasing RMP dosage: 75% (69/92) in R10, 82.5% (66/80) in R15 and 83.1% (76/91) R20 patients (\( P = 0.16 \)).

C O N C L U S I O N S: No significant increase in adverse events occurred when the RMP dose was increased from 10 mg/kg to 15 mg/kg or 20 mg/kg.

K E Y W O R D S: tuberculosis; treatment; rifampicin; toxicity.

T H E I N T R O D U C T I O N O F N E W D R U G S for routine treatment of drug-susceptible tuberculosis (TB) will take many years. Meanwhile, there may be an opportunity to improve treatment by the better use of available drugs, helped in part by the use of systems for grading adverse events.1,2 Rifampicin (RMP, R) is responsible for killing the majority of the tubercle bacilli in tuberculous lesions.3 When introduced in the 1970s, it was given at the lowest dose with proven efficacy, and this dosage has not been changed since.

The standard 6-month regimen recommended by the World Health Organization (WHO) is highly effective and safe.4 However, its efficacy depends on the administration of RMP throughout the 6-month period.4,5 In 1981, Wallace Fox wrote, ‘It is clear that 6-month regimens are too long. Higher dosage schedules, particularly of RMP, might be given.’6 In 2003, Pelouquin suggested that the current dose of 10 mg/kg was suboptimal, and recommended that higher doses be investigated.7 Higher RMP dosing is supported by animal models and early bactericidal activity data.8,9

The reluctance to investigate higher doses of RMP is due to the fear of serious hepatotoxic adverse effects. Little is known about the potential toxicity of a higher dose of RMP, as most data are derived from non-comparative cohort studies.10–15 A systematic review of 14 randomised trials using higher doses of RMP showed that hepatotoxicity was rarely observed.16 However, the authors state that ‘additional data on safety will be needed’.

The objective of the present study was to assess the safety of higher doses of RMP, 15 or 20 mg/kg/daily, vs. the standard 10 mg/kg dose when prescribed for the first 16 weeks of the standard 26-week treatment regimen to human immunodeficiency virus (HIV) non-infected patients with newly diagnosed micro-
copy-positive pulmonary TB. A secondary objective was to determine if the increased dose resulted in more rapid lung sterilisation, assessed by the culture conversion rate after 8 weeks of treatment. We report the results in 300 patients included in an open-label, randomised clinical trial, the RIFATOX Trial.

STUDY POPULATION AND METHODS

The study protocol was approved by the Oxford Tropical Research Ethics Committee (OxTREC, University of Oxford, Oxford, UK) and the ethics and regulatory review bodies of each participating centre.

Population

Newly diagnosed microscopy-positive adults in Santa Cruz (Bolivia), Kathmandu (Nepal) and Mbarara (Uganda) were invited to participate provided they met the eligibility criteria and provided informed consent. All enrolled patients were tested for hepatitis C antibody and hepatitis B surface antigen.

Eligibility criteria

Eligible patients were aged 18–65 years, had two sputum samples positive for tubercle bacilli on microscopy, had received less than a month of previous anti-tuberculosis chemotherapy and had a microscopy, had a reliable and accessible home address. Previous anti-tuberculosis chemotherapy and had a microscopy, had received less than a month of previous anti-tuberculosis chemotherapy and had a microscopy, had a reliable and accessible home address.

Patients were excluded if they were critically ill, had extra-pulmonary TB, were alcoholic, were pregnant or had psychiatric illness, blood disorders, diabetes, epilepsy, peripheral neuritis, haemoglobin <7 g/dl, serum alanine transferase (ALT) levels >5 times the upper limit of normal (ULN), creatinine clearance <30 ml/min, and isoniazid (INH, H) or RMP resistance (GenoType MTBDRplus test [Hain Lifescience, Nehren, Germany] or drug susceptibility testing on culture). HIV-positive patients were excluded because of possible interactions between antiretrovirals (ARVs) and high-dose RMP, leading to the reduction in blood levels of some ARVs.

Randomisation

A randomisation schedule was created by an independent person. Patients were randomised in a 1:1:1 ratio in blocks of nine patients to the three treatment groups, each comprising 100 subjects. Participating centres were supplied with a batch of sealed, serially numbered opaque envelopes, each containing a slip of paper showing the allocated regimen. No attempt was made to conceal the treatment regimen after randomisation from patients, researchers or health care staff. However, the laboratory staff and an independent clinician who would make a clinical assessment of any serious adverse event (SAE) were blinded to the regimen.

Stopping rule

The following stopping rule was applied to the trial: if, at review by the Data and Safety Monitoring Committee, ≥5 grade 4 events had occurred in one arm of the study, that arm would be discontinued.

Treatment

Three hundred eligible patients were randomised to the following regimens: 1) the control regimen (R10), comprising 8 weeks of daily ethambutol (EMB, E), INH, RMP and pyrazinamide (PZA, Z), followed by 18 weeks of daily INH and RMP (2EHRZ/4HR); 2) Study Regimen 1 (R15), comprising 8 weeks of daily EHRZ, followed by 18 weeks of daily HR, supplemented by 300 mg RMP for the first 16 weeks (2EHR15Z/2HR15/2HR); and 3) Study Regimen 2 (R20), comprising 8 weeks of daily EHRZ, followed by 18 weeks of daily HR, supplemented by 450 mg or 600 mg of RMP for the first 16 weeks (2EHRZ15Z/2HR15/2HR). The drugs given were those used in routine practice in Kathmandu and Santa Cruz. In Kathmandu, the drug formulations are EHRZ (275/75/150/400 mg) and HR (150/300 mg), and are supplied by the Global Drug Facility. RMP 150/300 mg was manufactured by Ranbaxy, Mumbai, India. In Santa Cruz, the formulations are E 400 mg (MacLeods, Mumbai, India), HR 150/300 mg, Z 400 mg and R 300 mg (Lupin, Mumbai, India). In Mbarara, drugs were imported for the purposes of the trial (EHRZ 275/75/150/400 mg) and HR (150/300 mg), and are supplied by the Global Drug Facility. RMP 150/300 mg was manufactured by Ranbaxy, Mumbai, India.

Doses were calculated at enrolment according to WHO weight bands: 35–39, 40–54, 55–69 and ≥70 kg, with targets of 5 mg/kg for INH, 25 mg/kg for PZA and 15 mg/kg for EMB. The target dose for RMP and the range for each weight band are shown in Table 1.

Follow-up

For the first 8 weeks, the patients attended the treatment centre daily for direct observation of doses ingested. Thereafter, the patients either attended 6 days a week (Kathmandu) or were given a supply of the drugs to be taken under the supervision of a designated family or community member, known as the Domiciliary Treatment Monitor (DTM) (Santa Cruz and Mbarara). The type of supervision was recorded on the treatment card for the first 16 weeks: C for treatment centre, D for DTM, T for unsupervised and N for not taken.

The patients were interviewed regarding symptoms and signs, and serum ALT levels were measured at 2, 4, 8, 12 and 16 weeks. Patients could also attend any time if they experienced side effects. A doctor

*Numbers before the letters indicate the duration in months of the phase of treatment; numbers in subscript indicate the trial regimen.
who was independent of the trial and blinded to the regimen was appointed to interview patients who reported symptoms or adverse reactions to assess their causality.

Sputum microscopy and *Mycobacterium tuberculosis* culture were performed pre-treatment and at 8 weeks using Löwenstein-Jensen medium. Drug susceptibility testing (DST) against INH and RMP were performed using either standard phenotypic tests (Kathmandu and Santa Cruz) or the Hain MTBDRplus test (Mbarara).17

**Data management**

Data were collected on case report forms. From Kathmandu and Santa Cruz, the forms were sent to St George’s, University of London, London, UK, where they were checked for missing and atypical results. Once these issues had been resolved, the forms were sent to Epicentre, Mbarara, where double data entry and data validation was carried out using Voozanoo software version 3.4.2 (Epiconcept, Paris, France).

**Site monitoring**

The sites were regularly monitored by the Trial Manager as well as local monitors.

**Outcome measures**

**Primary outcome**

The primary outcome was the occurrence of any grade 3 or 4 adverse event (AE) of the ‘Table for grading severity of adult adverse experiences’ (US Department of Health and Human Services, Division of AIDS [DAIDS])1 and/or SAE2 during the first 16 weeks of chemotherapy.

**Secondary outcomes**

Secondary outcomes were as follows: 1) culture conversion at the end of 8 weeks of chemotherapy, 2) treatment modification as a result of an SAE and/or a grade 3 or more AE, 3) any increase in ALT level at any time during treatment, and 4) the number of observed doses of chemotherapy ingested.

**Statistical methods**

**Sample size**

The decision to enrol a total of 300 patients was a pragmatic one based on the consideration that this would be sufficient to assess whether moving forward to a Phase III trial with higher doses of RMP could be justified on safety criteria. A study with 100 controls and 200 test cases has 82% power to detect the difference between a major AE rate of 5% in controls and 16% in test cases at two-sided 5% significance level.

**Analysis**

Safety analysis was performed among patients who received at least one dose of treatment. Hepatotoxicity was assessed using serial ALT measurements and graded using the DAIDS1 system according to the range of normal levels for each laboratory. Non-hepatic AEs were similarly graded. Efficacy was assessed by the rate of sputum culture negativity after 8 weeks of treatment.

**Adherence**

Adherence to prescribed doses was ensured by observing drug ingestion by the medical staff and DTM.

**RESULTS**

**Patient enrolment**

Enrolment began in February 2011 and ended in May 2013. Three hundred patients were enrolled (100 per arm); 150 in Bolivia, 50 in Nepal, and 100 in Uganda.

**Baseline characteristics, and treatment supervision**

The Figure shows the populations available for analysis. Baseline characteristics were similar in the three groups (Table 2). Two thirds were males. The median age was approximately 30 years, and median weight approximately 50 kg. Less than 3% of patients were positive for either hepatitis B surface antigen or hepatitis C antibody. The median RMP dose was respectively 9.6, 15 and 18.8 mg in the three RMP groups.

**Safety**

**Primary outcome analysis**

A total of seven grade 3 AEs were recorded in respectively 1.0% (1/100), 2.0% (2/100) and 4.0% (4/100) of the R10, R15 and R20 patients (trend test \( P = 0.15 \)). Of the 1800 scheduled ALT tests, results were available on 1719 occasions. Table 3 shows the

<table>
<thead>
<tr>
<th>Weight kg</th>
<th>Control regimen 10 mg/kg (FDC)</th>
<th>Study regimen 15 mg/kg (add 2 RMP capsules)</th>
<th>Study regimen 20 mg/kg (add 3 or 4 RMP capsules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35–39</td>
<td>7.7</td>
<td>15.4</td>
<td>19.2</td>
</tr>
<tr>
<td>40–54</td>
<td>8.3</td>
<td>14.0</td>
<td>16.7</td>
</tr>
<tr>
<td>55–69</td>
<td>8.7</td>
<td>13.0</td>
<td>17.4</td>
</tr>
<tr>
<td>≥ 70</td>
<td></td>
<td>10.7</td>
<td>15.4</td>
</tr>
</tbody>
</table>

*Received 3 capsules.

RMP = rifampicin; FDC = fixed-dose combination.

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**Table 2**

RIFATOX Trial: target range of RMP drug dosages per kg by weight band

<table>
<thead>
<tr>
<th>Weight kg</th>
<th>Control regimen 10 mg/kg (FDC)</th>
<th>Study regimen 15 mg/kg (add 2 RMP capsules)</th>
<th>Study regimen 20 mg/kg (add 3 or 4 RMP capsules)</th>
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<td>35–39</td>
<td>7.7</td>
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</tr>
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<td>40–54</td>
<td>8.3</td>
<td>14.0</td>
<td>16.7</td>
</tr>
<tr>
<td>55–69</td>
<td>8.7</td>
<td>13.0</td>
<td>17.4</td>
</tr>
<tr>
<td>≥ 70</td>
<td></td>
<td>10.7</td>
<td>15.4</td>
</tr>
</tbody>
</table>

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results in each grade. The majority remained within the laboratory’s normal range and are graded as 0. ALT levels increased as the dose of RMP increased, most to grades 1 and 2.

One patient (R15) who received 750 mg daily RMP developed jaundice after 34 doses with a grade 3 ALT (192 international units [IU]) increase and a cutaneous hypersensitivity reaction, necessitating interruption of treatment. When all symptoms and signs had subsided and ALT levels had returned to normal, he was restarted on the standard regimen and completed 6 months of treatment. In the remaining six cases, ALT levels returned to normal at the next visit without treatment interruption. There were no ALT increases to grade 4. No increases above grade 2 were recorded in patients positive for hepatitis B surface antigen or hepatitis C antibody.

Table 4 shows the frequency of non-hepatic AEs reported in all three regimens. SAEs occurred in two patients. One (R15) patient, diagnosed with carcinoma of the oesophagus after 12 weeks of treatment, was withdrawn from the trial. His culture result at 8 weeks was positive. A second (R20) patient died of septicaemia at 12 weeks after starting treatment. His culture result at 8 weeks was negative. For all other events, none was greater than grade 2, and all were treated symptomatically, without treatment interruption.

Table 2  Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>R10 (n = 100)</th>
<th>R15 (n = 100)</th>
<th>R20 (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n</td>
<td>66</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>Age, years, median (range)</td>
<td>28.5 (16–67)</td>
<td>27.5 (16–67)</td>
<td>30 (19–66)</td>
</tr>
<tr>
<td>Body weight, kg, median (range)</td>
<td>50.7 (35–87)</td>
<td>53 (39–79)</td>
<td>51.55 (38–81)</td>
</tr>
<tr>
<td>Baseline ALT, IU/l, median (range)</td>
<td>17.1 (4–160)</td>
<td>19.1 (5–133)</td>
<td>17 (5–110)</td>
</tr>
<tr>
<td>Haemoglobin, g/l, median (range)</td>
<td>11.65 (6–15.0)</td>
<td>12.1 (8–18.1)</td>
<td>11.8 (8.3–15.9)</td>
</tr>
<tr>
<td>Creatinine clearance, median (range)</td>
<td>79.16 (40.75–149.23)</td>
<td>78.64 (35.24–233.80)</td>
<td>81.1 (40.1–250.5)</td>
</tr>
<tr>
<td>Hepatitis B-positive, n</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hepatitis C-positive, n</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hepatitis B and C-positive, n</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Daily RMP dose, median (range)</td>
<td>9.6 (7.7–11.8)</td>
<td>15.0 (12.5–18.3)</td>
<td>18.8 (14.4–25.5)</td>
</tr>
</tbody>
</table>

* R10 = 2EHRZ/4HR; R15 = 2EHR15Z/2HR15/2HR; R20 = 2EHR20Z/2HR20/2HR, where numbers before the letters indicate the duration in months of the phase of treatment; numbers in subscript indicate the study regimen.

1 Calculated as: [(140–age) × weight × 1.23 (0.85 if female)]/serum creatinine [µmol/l].

ALT = alanine transferase; IU = international units; RMP = rifampicin; E = ethambutol; H = isoniazid; Z = pyrazinamide.
### Table 3 Grading of ALT values recorded at any time during the trial by study regimen

<table>
<thead>
<tr>
<th>Grade†</th>
<th>R10* (n = 600)</th>
<th>R15* (n = 600)</th>
<th>R20* (n = 600)</th>
<th>Total (n = 1800)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>553 (92)</td>
<td>501 (84)</td>
<td>518 (86)</td>
<td>1572 (87)</td>
</tr>
<tr>
<td>1</td>
<td>29 (5)</td>
<td>51 (9)</td>
<td>42 (7)</td>
<td>122 (7)</td>
</tr>
<tr>
<td>2</td>
<td>2 (0.3)</td>
<td>8 (1.3)</td>
<td>8 (1.3)</td>
<td>18 (1)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0)</td>
<td>2 (0.3)</td>
<td>4 (0.6)</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Results not available</td>
<td>15 (2.5)</td>
<td>38 (6.3)</td>
<td>28 (5)</td>
<td>81 (5)</td>
</tr>
</tbody>
</table>

* R10 = 2EHRZ/4HR; R15 = 2EHR15Z/2HR15/2HR; R20 = 2EHR20Z/2HR20/2HR, where numbers before the letters indicate the duration in months of the phase of treatment; numbers in subscript indicate the study regimen.
† Based on DAIDS grading as follows: 1 grade 1 = laboratory range 1.25–3.0 × ULN; grade 2 = >3.0–5.0 × ULN; grade 3 = >5.0–10.0 × ULN; grade 4 = >10.0 × ULN. ALT = alanine transferase; E = ethambutol; H = isoniazid; R = rifampicin; Z = pyrazinamide; DAIDS = Division of AIDS (National Institutes of Health, Bethesda, MD, USA); ULN = upper limit of normal.

### Efficacy

Baseline cultures were missing in all three arms (Figure) and, together with those with initial INH resistance, these participants were excluded from the analysis as late screening failures. The 8-week culture result was unavailable for 16 patients, either because they were contaminated or they were not performed because patients could not provide sputum, leaving 92 R10, 80 R15 and 91 R20 patients for analysis.

Culture negativity rates were respectively 75% (69/92), 82.5% (66/80) and 83.1% (76/91) (trend test P = 0.16). A logistic regression of culture conversion was performed using dose as a continuous predictor and treatment centre as nominal predictor. The analysis showed a 0.71-fold (29%) reduction in the odds of having a positive result given a 5 mg/kg increase in dose (confidence interval [CI] 0.47–1.06, P = 0.09).

### Adherence

In Kathmandu, 76% of all doses ingested were observed by the medical staff, whereas 80% of the supervision in Mbarara was carried out by the DTM. In Santa Cruz, 66% of dose ingestion was observed by the medical staff and 30% by the DTM.

### DISCUSSION

In this trial, RMP at daily doses of 15 mg/kg and 20 mg/kg for the first 16 weeks in microscopy-positive HIV-negative patients with pulmonary TB showed a rising, but statistically non-significant, trend in ALT levels that returned to normal without treatment interruption. Increasing RMP doses also showed a non-significant increasing trend in culture conversion at 8 weeks.

The occurrence of jaundice and increase of ALT to 192 IU (grade 3) necessitated treatment interruption in only one patient who was receiving RMP at 15 mg/kg. It is possible that some of the hepatic AEs observed in this trial are attributable to the use of INH or PZA rather than RMP. In a trial comparing two 8-month regimens with the standard 6-month regimen, where RMP was given at the standard dose,5 10/1355 (0.7%) trial patients experienced hepatic side effects, leading to an interruption of treatment of >7 days. Only 4/10 patients were on RMP, whereas all were on INH, suggesting that some of these hepatic events were more likely to be related to INH. Similar conclusions were made in two other reports.17,18

Patients infected with hepatitis B and hepatitis C (n = 14) had no recorded increases in ALT value. However, the numbers are too small to allow any comment on safety. All but one of the increases in ALT were transient, returning to normal at the next recorded test. Almost identical results are reported in an abstract.19 Similar results are reported by the PanACEA MAMS-TB Trial20 in groups of 62 patients, each treated with 12 weeks of RMP at up to 35 mg/kg/day. Grade 3 or higher AEs were reported in 12% of the R10, 12% of the R20, and 14% of the R35 (35 mg/kg/d) group.

Culture negativity rates at 8 weeks showed an increase (albeit non-significant) with increasing dose. However, although the trial was not powered to determine an effect on culture conversion, the CI of the logistic regression does not exclude the possibility of a substantial improvement with increasing dose. One limitation of our study was that it was an open-label trial without a placebo, and patients and staff were aware of treatment
allocations. However, as we used microbiological and laboratory (ALT) outcomes, and the clinician responsible for decisions relating to treatment modification was blinded to study allocation, we feel that bias had been minimised. Second, the drugs used were those in use for routine treatment in each country. This allowed us to carry out the trial as a pragmatic, operational study at a minimum cost and within a short time-frame. Third, the trial was conducted in HIV-negative patients whose tolerability level may have been different from that of HIV-positive patients. Fourth, the absence of pharmacokinetic assessments failed to give an indication of blood levels attained with higher doses of RMP and whether there were any interracial differences. However, as the patients were from different races, the similar outcomes in all three arms supports the external validity of the trial. Finally, methods used for treatment administration and directly observed treatment differed between centres, although, importantly, this did not result in a difference in losses to follow-up or in the number of doses taken.

CONCLUSION

A daily dose of 20 mg/kg RMP for 4 months appears to be safe and well tolerated. Although the treatment groups are relatively small, these encouraging results suggest that a daily dose of 20 mg/kg RMP for 4 months is safe enough to be taken forward to larger Phase III trials. However, caution should be exercised in patients whose liver function tests are compromised for any reason, in those with viral hepatitis infection and in pregnant women.

Acknowledgements

The authors are grateful to Epicentre/Médecins Sans Frontieres (MSF) (Paris, France) for supporting all trial-related activities in Mbarara, Uganda.

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RIFATOX Trial Team: A Jindani (Chief Investigator), T Harrison, G Borgulya, D Mitchison, N Patel, F Dubash, A Checkley (Institute for Infection and Immunity, St George’s, University of London, London, UK); B Shrestha (Principal Investigator [PI]), S Tandukar, N Mitra Shrestha, D Joshi, S Maharjan and B Maharjan (German Nepal Tuberculosis Project, Kathmandu, Nepal); L Westermann de Patiño, T Gonzales, R A de Fernandes (PIs); M Ortiz, N Cortéz, I Bozo, Y Qantana, D Senzano (Centros Broncopulmonares, Cruz Roja, Santa Cruz, Bolivia); M Burgos (Tuberculosis Program, University of New Mexico, Albuquerque, NM, USA); D Atwine (PI), M Nansumba, P Oririkiza, P Boonabaana, D Akatuhebwa, M Riera, Y Boum II, W Benda, R Arinaiwte, S Logoose, J Mwanga-Amumapeire (MSF/ Epicentre, Mbarara, Uganda); M Bonnet (Epicentre, c/o MSFCH, Geneva, Switzerland).

Trial Steering Committee: H Hodgson, D Moore, M Bonnet, M Burgos.

Data and Safety Monitoring Committee: G Davies, S White, J Porter.

Conflicts of interest: none declared.

References

1 US Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Table for grading severity of adult adverse experiences. Bethesda, MD, USA: US Department of Health and Human Services, 1992.


**CONTEXTE :** Essai clinique randomisé de phase IIB.

**OBJECTIFS :** Evaluer si l’augmentation de la dose de rifampicine (RMP) de 10 mg/kg à 15 ou 20 mg/kg augmente les effets secondaires graves en général (SAE) et/ou les effets secondaires hépatiques de grade 3 ou 4.

**MÉTHODES :** Trois cents patients négatifs pour le virus de l’immunodéficience humaine, atteints de tuberculose (TB) pulmonaire récemment diagnostiquée, à microscopie positif, ont été assignés de manière aléatoire à un des trois protocoles suivants : Protocole témoin (R10), éthambutol (EMB), isoniazide (INH), RMP et pyrazinamide chaque jour pendant 8 semaines suivi par INH et RMP chaque jour pendant 18 semaines. Protocole d’étude 1 (R15), comme ci-dessus avec la dose de RMP augmentée à 15 mg/kg de poids pendant les 16 premières semaines. Protocole d’étude 2 (R20), comme ci-dessus avec la RMP augmentée à 20 mg/kg. Des dosages d’alanine transférase (ALT) sérique ont été réalisés à intervalles réguliers.

**RÉSULTATS :** Il y a eu sept augmentations de grade 3 du taux d’ALT, 1/100 (1%) dans le protocole R10, 2/100 (2%) dans le protocole R15 et 4/100 (4%) dans le protocole R20 (test de tendance, $P = 0,15$). Un patient a développé un ictere (R15), nécessitant une modification du traitement. Il n’y a pas eu d’augmentation de grade 4 de l’ALT. Il y a eu une augmentation non significative du taux de négativisation de la culture à 8 semaines avec l’accroissement de la dose de RMP, 75% (69/92) pour R10, 82,5% (66/80) pour R15 et 83,1% (76/91) pour R20 ($P = 0,16$).

**CONCLUSION :** Aucune augmentation significative des effets secondaires n’est survenue quand la dose de RMP a été augmentée de 10 mg/kg à 15 mg/kg ou 20 mg/kg.