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First-line tuberculosis treatment with double-dose rifampicin is well tolerated

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SUMMARY

OBJECTIVE: To compare the occurrence of unfavourable treatment and safety outcomes of double-dose rifampicin (RMP; 20 mg/kg/d, intervention) with standard dose (10 mg/kg/d, control) in a first-line tuberculosis (TB) treatment regimen for smear-positive TB patients in Bangladesh.

DESIGN: This was a randomised clinical trial. The primary efficacy and safety endpoints were the occurrence of an unfavourable treatment outcome (death, failure, relapse or loss to follow-up) and the occurrence of any serious drug-related adverse event (SAE).

RESULTS: In primary efficacy analysis, among 343 control and 347 intervention patients, respectively 15.5% and 11.8% had an unfavourable outcome. In safety analysis, among 349 intervention and 352 control patients, respectively 4.3% and 2.6% experienced an SAE. These differences were not significant. There was a significantly lower occurrence of SAEs, explained by a lower occurrence of hepatic toxicity, in a RMP double-dosed but erroneously HZE (isoniazid+pyrazinamide+ethambutol) under-dosed subgroup.

CONCLUSIONS: Our findings show that there is no statistically significant difference in terms of efficacy and safety between standard and double-dose RMP. An accidental finding (related to dosage levels of the standard regimen) suggests that high-dose RMP is potentially a lesser cause of hepatotoxicity. Larger trials with more power, or trials with at least a triple-dose might be needed to clearly see the effect of high-dose RMP on unfavourable outcomes.

KEY WORDS: drug dosage; hepatotoxicity; safety; efficacy; relapse-free treatment success

RIFAMPICIN (RMP, R) IS THE CORE drug of first-line tuberculosis (TB) treatment regimens.[1] Although for standard dose levels its early bactericidal activity (EBA) is surpassed by isoniazid,[2] RMP is the driving drug because of its potent sterilising activity, which lasts throughout treatment.[3]

The World Health Organization (WHO) currently recommends a daily dose of 10 mg/kg RMP in adults.[4] This is the minimum effective dose and was selected due to the high cost of RMP and the fear for dose-related adverse events.[5] However, as long ago as 1969 the activity of RMP had been reported as strongly dose-dependent, with proportionally stronger activity when increasing its dose up to 40 mg/kg in mice.[6] The late Dr Mitchison drew attention to the potential superior effectiveness of high-dose RMP, which is possibly related to its higher peak concentration.[7] Recent studies showed that a dose of up to 35 mg/kg RMP was safe when administered during a few weeks to months.[8–10] Moreover, early outcomes, such as time to culture conversion, were better among those treated with high-dose RMP.[8,11]

To our knowledge, no previous trial has assessed the effect of double-dose RMP on relapse-free treatment success. This is the first large-scale trial to compare double-dose with standard-dose RMP in terms of occurrence of unfavourable treatment outcomes and safety under control programme conditions.

METHODS

Study design

This open-label 1:1 parallel randomised clinical trial was conducted in eight large diagnostic and treatment centres run by the Damien Foundation (DF) Bangladesh Project. The HIV prevalence among TB patients was about 0.1%.[12]

Sample size

With a sample size of 500 in each arm, a reduction from 10% to 6.5% of unfavourable outcomes would

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result in a significant P value ($P < 0.05$), and an increase with at least 2% hepatotoxicity compared to the control arm would attain statistical significance ($P < 0.05$).

Study population

Patients aged ≥15 years with smear-positive pulmonary TB were included after obtaining written informed consent. Exclusion criteria were RR-TB at diagnosis, need for hospitalisation because of poor clinical condition, clinically active liver disease, known hepatitis B or C or HIV infection, and pregnancy.

Study regimens

Patients were randomised to the control regimen (the standardised 6-month regimen with 2 months of ethambutol (E) and pyrazinamide (Z, PZA), isoniazid (H, INH) and RMP10 mg/kg for the entire duration (WHO Cat. 1: 2EHRZ/4HR)), or to the study regimen, with an additional 10 mg/kg RMP throughout. Randomisation was stratified by centre and by type of case (new or retreatment) and blocked (block size 10). Randomisation was performed using sealed envelopes.

Following an erroneously made bench aid, the 33–41 kg intervention group was administered two rather than three fixed-combination RHZE tablets, plus 450 mg, rather than 300 mg RMP. Thus, intervention patients in the 33–41 kg group received only two thirds of the standard HZE dose. All other patients in the intervention and control arm received the standard HZE dose. This error did not affect the double RMP dosing.

In both arms, patients were treated under daily observation at the DF clinic or near their homes, mostly by trained village doctors. All patients were monitored clinically at each visit, and screened for hepatotoxicity using an alanine aminotransferase (ALT) test at 0, 2, 4 and 8 weeks of treatment. All drugs had to be stopped if transaminases increased to >5 times the upper limit of normal (ULN) (34/45 IU for females/males at all study laboratories). Aspartate aminotransferase (AST) was tested additionally if ALT was raised above the ULN. After 8 weeks, hepatitis was suspected on clinical basis only. Patients with elevated transaminases or clinical signs of hepatotoxicity were referred to medical officers at the referral hospital for further liver function tests and management. Drugs were re-introduced sequentially when ALT had dropped below 2 ULN or jaundice had disappeared. No limit was set on the maximum time of interruption. Blood counts were not monitored systematically. Patients with delayed sputum smear microscopy conversion before 5 months of treatment were checked using Xpert®MTB/RIF (Cepheid, Sunnyvale, CA, USA) drug susceptibility testing (DST), and switched to multidrug-resistant TB (MDR-TB) treatment if suspected RMP resistance was confirmed. From 5 months onwards, auramine acid-fast smear positivity was a sufficient criterion to declare failure of treatment, followed by DST and appropriate retreatment.

Laboratory procedures

Auramine staining was performed as recommended by the WHO and the Global Laboratory Initiative.[13] Serum transaminase was tested at the DF hospital laboratories from cold chain-transported samples. External quality assurance was performed by INSTAND, Dusseldorf, Germany. Sputum from smear-defined failure and relapse cases was referred for conventional culture and DST (proportion method),[14] in addition to rapid Xpert screening. Standard procedures were used for decontamination (modified Petroff), centrifugation and inoculation on Löwenstein-Jensen medium (LJ). Non-tuberculous mycobacteria isolated were identified using 16S rRNA sequence analysis.

Smear-positive baseline sputum specimens and failure or relapse sputa were preserved in 2 ml cryovials using ethanol 70% final concentration for a posteriori *rpo*B gene sequencing at the Institute of Tropical Medicine, Antwerp, Belgium (ITM). Failure, relapse and 12-month follow-up sputum samples were sent to the DF reference laboratory for culture and DST. Culture isolates were referred to the ITM for genotyping and DNA sequencing.

Genotyping was performed by spoligotyping, 24-loci MIRU VNTR (mycobacterial interspersed repetitive unit-variable number of tandem repeats) and/or Deeplex® MycTB (Genoscreen, Lille, France) on pairs for confirmation of strain identity of all recurrences to exclude reinfection and to confirm presumed acquired resistance.[15]

For sequencing of the *rpo*B gene, all known resistance-conferring sequences were targeted using extended primers. Additional resistance was tested using first- and second-line line-probe assay (Hain Genotype MTBDR*Plus* and MTBDR*sl*, Hain Lifesciences, Nehren, Germany) when an *rpo*B mutation had been detected.

Study endpoints and data analysis

The primary efficacy endpoint was the occurrence of unfavourable treatment outcomes (either relapse, failure, death or loss to follow-up during treatment) against relapse-free treatment success. Relapse and failure were smear-defined (any number of acid-fast bacilli [AFB]).[16] Relapse-free treatment success was assessed clinically and by sputum AFB smear and culture 12 months after cure or treatment completion. Secondary, smear-defined failures and relapses were corrected for results of culture, vital staining and ITM laboratory results. The primary safety endpoint was the occurrence of any serious adverse event (SAE) and grade 3–4 hepatotoxicity, defined as transami-

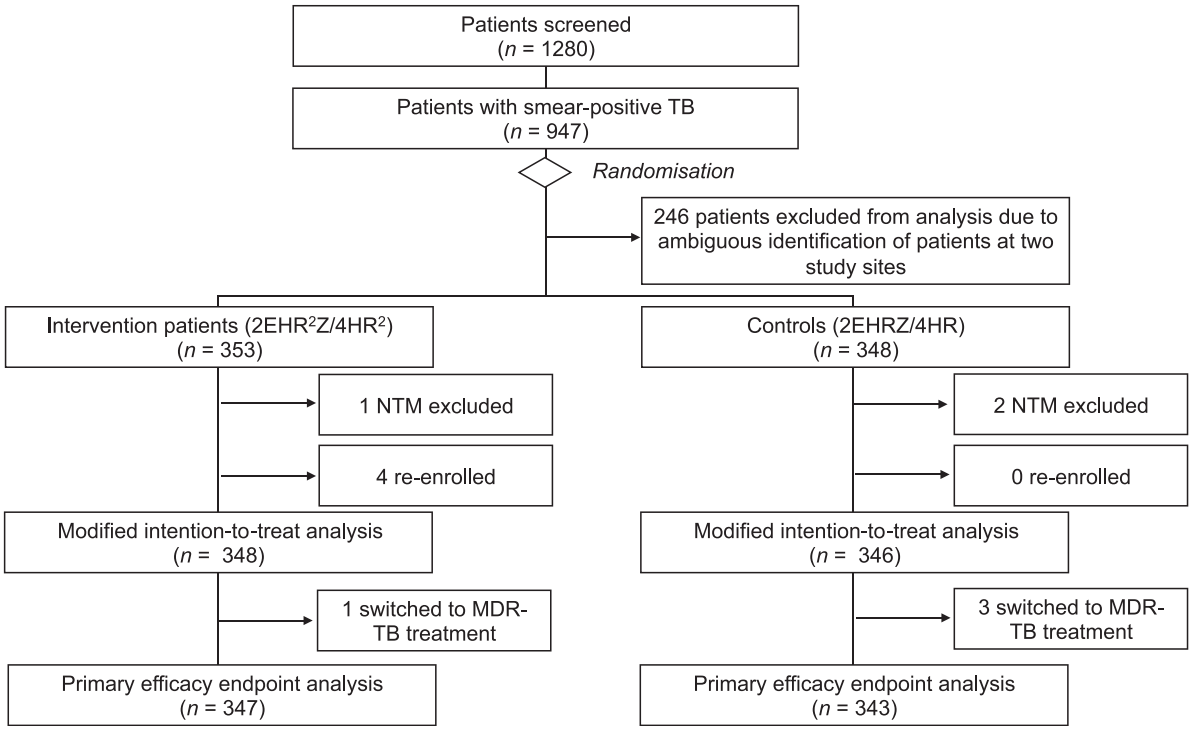

Figure Flowchart enrolment and inclusion in efficacy analysis. TB = tuberculosis; E = ethambutol; H = isoniazid; R = rifampicin; R^2 = double-dose rifampicin; Z = pyrazinamide; NTM = non-tuberculous mycobacteria; MDR-TB = multidrug-resistant tuberculosis.

nase increases to >5–20 ULN (grade 3) or >20 ULN (grade 4).[17] SAE were categorised as drug-related by the investigators after exchange with the treating clinicians. The safety analysis included all patients who received at least a dose, and according to the regimen actually received.

The primary efficacy endpoint analysis excluded patients diagnosed with non-tuberculous mycobacteria (NTM) at baseline, those enrolled for a second time, or diagnosed with RR and switched to MDR-TB treatment before the fifth treatment month (see Figure). In modified intention to treat analysis (mITT), described upfront in a statistical analysis plan, patients with a successful 6-month treatment outcome but without 12-month post-treatment follow-up were counted as having an unfavourable outcome, but as cure/completed for routine TB control programme evaluation (hereafter called "observational analysis"). Poor adherence was not a criterion for exclusion from analysis. Missed doses led to an equivalent extension of treatment. Patients absent for at least 2 months were classified as lost to follow-up during treatment.

The confidence intervals (CIs) of proportions were calculated using Wilson's score method.[18] To estimate the size of the effect, adjusted odds ratios with 95% CIs were calculated using a logistic regression model adjusted for "hospital" as fixed effect. To correct for incorrect dosing, the effect of RMP dosage on the occurrence of unfavourable treatment outcomes and safety endpoints was assessed adjusted for hospital, new/retreatment case, HZE dosage (the sum of H, Z and E dose in mg divided by the patient's weight in kg) and body-weight category (33–41 kg vs. other).

Ethical aspects

The study protocol, consent form and information sheet were approved by the National TB Programme of Bangladesh, the ethics review board of the Bangladesh Medical Research Council (Dhaka, Bangladesh; BMRC/NREC/2013-2016/215), the ITM Institutional Review Board (Antwerp, Belgium; 917/13), the University of Antwerp Ethics Review Board (Antwerp, Belgium; EC14/4/31), and the Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease (Paris, France; 94/13).

The trial was conducted in compliance with the Helsinki Declaration and ICH-GCP guidelines and was registered in clinicaltrials.gov as NCT02153528, where the study protocol was uploaded.

RESULTS

Of a total of 1280 patients screened, 947 patients were recruited and randomised. Due to frequent ambiguous identification of patients at two sites, shown during post-study laboratory analysis of their baseline sputa, all 246 patients enrolled at these sites were excluded from analysis (see Figure). Patients were recruited from 2 November 2014 until 30

Table 1 Characteristics of patients included in efficacy analysis*

	Intervention ($n = 352$)		Control ($n = 346$)	
	n	%	*n*	%
Age, years, median [IQR]	45	[28–55]	42	[28–55]
Female sex	92	(26.1)	95	(27.5)
Retreatment case	29	(8.2)	20	(5.8)
BMI, kg/m^2, median [IQR]	16.4	[15.2–17.8]	16.2	[15.1–18.0]
Weight, kg, median [IQR]	42	[36–46]	41	[37–46]
<33	31	(8.8)	22	(6.4)
33–41	140	(39.8)	156	(45.1)
>41	181	(51.4)	168	(48.6)
Diabetes	17	(4.8)	15	(4.3)
ALT > ULN	37	(10.5)	57	(16.5)
Correctly dosed†	212	(60.2)	346	(100.0)
Number of AFB (auramine) per 200x field at diagnosis, median [IQR]	90	[7–500]	98	[7–550]

* Characteristics of three persons with a non-tuberculous mycobacteria infection (1 intervention and 2 control patients) are not shown in this table.
† Due to an erroneous bench aid used in the study clinics, the 33–41 kg weight band in the intervention arm was given only 2/3 of the HZE dose given to the same weight band in the control arm.
IQR = interquartile range; BMI = body mass index; ALT = alanine aminotransferase; ULN = upper limit of normal; AFB = acid-fast bacilli; HZE = isoniazid+pyrazinamide+ethambutol.

September 2015. The final visit of the last patient was on 22 July 2017.

Baseline characteristics appeared very similar in both arms (Table 1). Supplementary Data Table S1 shows that the characteristics of excluded patients were similar to those of included patients.

Efficacy

After exclusion of four patients who were switched to MDR treatment before the fifth month, and four intervention patients who were re-enrolled, 347 intervention and 343 control patients were left for primary efficacy endpoint analysis (see Figure). In mITT analysis, 53 controls (15.5%; 95%CI 12.0–19.7) and 41 intervention patients (11.8%; 95%CI 8.8–15.6) of experienced an unfavourable outcome. In observational analysis, 28 controls (8.2%; 95%CI 5.7–11.5) and 28 intervention patients (8.1%; 95%CI 5.6–11.4) experienced an unfavourable outcome.

Treatment outcomes were similar for the RMP double-dosed/HZE under-dosed intervention subgroup (weight 33–41 kg) and the RMP double-dosed/HZE correctly dosed intervention subgroup (Table 2).

The association between the occurrence of unfavourable outcomes (mITT) and the use of the intervention regimen vs. the control regimen was non-significant (adjusted odds ratio [aOR 0.73], 95%CI 0.47–1.14; $P = 0.16$). Corrected for under-dosing in an intervention subgroup, the association between the occurrence of unfavourable outcomes (mITT) and RMP dosage (aOR 0.68, for every increase with 10 mg R/kg; 95%CI 0.41–1.11; $P = 0.12$) or HZE dosage (aOR 0.97, for every increase with 10 mg HZE/kg; 95%CI 0.70–1.35; $P = 0.87$) was not significant (Table 3). The difference in terms of relapse-free treatment success between intervention and control patients was non-significant in mITT analysis.

Correction of smear-based outcomes

Overall, 20 auramine smear-defined failures were reported. None of these 20 were true treatment failures. Culture was performed for 9 of 20 failure specimens: 8 remained negative and 1 showed NTM. For the 11 remaining smear-defined failures, no culture evidence was available, but all were classified as without true failure of treatment but secreting dead bacilli, since all were negative on vital staining while showing very few AFB in the auramine smear.

Twelve months post-treatment, five patients were identified with smear- or culture-based relapse. Three of these patients were positive on both smear and culture, one patient was smear-positive, but culture-negative and one patient was culture-positive, but smear-negative. Three *Mycobacterium tuberculosis*-positive follow-up culture isolates were recorded in the intervention arm and all were confirmed to be true relapses. One *M. tuberculosis*-positive follow-up isolate was recorded in the control arm, but this was found to be due to reinfection upon genotyping.

Safety

In total, 6.9% (24/349) of controls vs. 3.7% (13/352) of intervention patients developed an SAE; 4.3% (15/349) of controls vs. 2.6% (9/352) of intervention patients developed a drug-related SAE (Table 4). An increase of transaminases (>5 ULN) was recorded for 7 (2.0%) control vs. 3 (0.9%) intervention patients. No patient had a grade 4 increase of transaminases. Overall, differences between arms were not statistically significant.

Fewer drug-related SAE were found in the RMP double-dosed/HZE under-dosed intervention sub-

Table 2 Efficacy of standard and double-dose rifampicin, stratified by dosage

	Intervention		Control		
	n	(%; 95% CI)	*n*	(%; 95% CI)	aOR† (95% CI)
Total patients included in efficacy analysis	(*n* = 347)		(*n* = 343)		
Those with relapse-free success	306	(88.2%; 84.4–91.2)	290	(84.5%; 80.3–88.0)	
Those LTFU during treatment	8	(2.3%; 1.2–4.5)	8	(2.3%; 1.2–4.5)	
Those who died on treatment	5	(1.4%; 0.6–3.3)	11	(3.2%; 1.8–5.7)	
Those with treatment failure#	12	(3.5%; 2.0–5.9)	8	(2.3%; 1.2–4.5)	
Those who relapsed within 12 months#	3	(0.9%; 0.3–2.7)	1	(0.3%; 0.1–1.8)	
Those LTFU or with no sputum by 12 months	13	(4.0%; 2.4–6.8)	25	(7.9%; 5.4–11.4)	
mITT analysis: *unfavourable outcome	41	(11.8%; 8.8–15.6)	53	(15.5%; 12.0–19.7)	0.73 (0.47–1.14)
Observational analysis: unfavourable outcome§	28	(8.1%; 5.6–11.4)	28	(8.2%; 5.7–11.5)	0.99 (0.57–1.71)
Total patients who were correctly dosed ‡	(*n* = 210)		(*n* = 187)		
Those with relapse-free success	186	(88.6%; 83.6–92.2)	156	(83.4%; 77.4–88.1)	
Those LTFU during treatment	6	(2.9%; 1.3–6.1)	7	(3.7%; 1.8–7.5)	
Those who died on treatment	4	(1.9%; 0.7–4.8)	5	(2.7%; 1.1–6.1)	
Those with treatment failure#	5	(2.4%; 1.0–5.5)	5	(2.7%; 1.1–6.1)	
Those who relapsed within 12 months#	2	(1.0%; 0.3–3.7)	1	(0.6%; 0.1–3.3)	
Those LTFU or with no sputum by 12 months	7	(3.6%; 1.7–7.2)	13	(7.6%; 4.5–12.6)	
mITT analysis: *unfavourable outcome	24	(11.4%; 7.8–16.4)	31	(16.6%; 11.9–22.6)	0.62 (0.35–1.11)
Observational analysis: unfavourable outcome§	17	(8.1%; 5.1–12.6)	18	(9.6%; 6.2–14.7)	0.82 (0.41–1.64)
Total patients who were under-dosed‡	(*n* = 137)		(*n* = 156)		
Those with relapse-free success	120	(87.6%; 81.0–92.1)	134	(85.9%; 79.6–90.5)	
Those LTFU during treatment	2	(1.5%; 0.4–5.2)	1	(0.6%; 0.1–3.5)	
Those who died on treatment	1	(0.7%; 0.1–4.0)	6	(3.8%; 1.8–8.1)	
Those with treatment failure#	7	(5.1%; 2.5–10.2)	3	(1.9%; 0.7–5.5)	
Those who relapsed within 12 months#	1	(0.8%; 0.1–4.3)	0	(0.0%)	
Those LTFU or with no sputum by 12 months	6	(4.7%; 2.2–9.9)	12	(8.2%; 4.8–13.8)	
mITT analysis: *unfavourable outcome	17	(12.4%; 7.9–19.0)	22	(14.1%; 9.5–20.4)	0.85 (0.43–1.69)
Observational analysis: unfavourable outcome§	11	(8.0%; 4.5–13.8)	10	(6.4%; 3.5–11.4)	1.22 (0.50–2.99)

† Adjusted for hospital, new/re-treatment case and the effect on occurrence of serious adverse events was adjusted for hospital using a logistic regression model.
# Failure and relapse based on positive smear for acid-fast bacilli but not necessarily with positive culture.
* Patients without post-treatment follow-up were considered to have experienced an unfavourable outcome.
§ Patients without post-treatment follow-up are considered to have experienced a favourable programmatic outcome, as 1) relapses were rare, 2) in routine care, no post-treatment follow-up was conducted, 3) Damien Foundation (DF) was recognised as the main provider, and severely sick people likely would return to the DF clinic.
‡ Due to an erroneous bench aid used in the study clinics, patients in the 33–41 kg weight band of the intervention arm was given only 2/3 of the HZE dose given to the same weight band in the control arm.
CI = confidence interval; aOR = adjusted odds ratio; LTFU = lost to follow-up; MITT = modified intention to treat; H = isoniazid, Z = pyrazinamide, E = ethambutol.

group (weight 33–41 kg) than in the normal-dosed control subgroup (aOR 0.28, 95%CI 0.06–0.97; Table 4). In the RMP double-dosed/HZE under-dosed subgroup zero patients experienced grade 3–4 hepatotoxicity, whereas 2.6% of the normal-dosed control subgroup of the same weight-band experienced grade 3–4 hepatotoxicity (Table 4). The association between the occurrence of drug-related SAE and RMP dosage was not significant (aOR 1.20, for every increase with 10 mg R/kg; 95% CI 0.43–3.31; $P = 0.73$). However, the odds of drug-related SAE doubled (aOR 1.91, for every increase with 10 mg HZE/kg; 95%CI 1.05–3.51; $P = 0.04$) (Table 3).

DISCUSSION

This trial is the first to compare a double-dose of RMP with a standard dose in terms of occurrence of unfavourable outcomes and safety in a large number of TB patients under controlled programme conditions. Double- and standard dose RMP-based first-line treatment regimens were not statistically significantly different in terms of occurrence of unfavourable outcomes and safety. We did not find any evidence of increased hepatotoxicity, concordant with reports from previous studies on a smaller numbers of patients.[8,10,11]

Table 3 Predictors of an unfavorable outcome and serious adverse events

	Unfavourable treatment outcome (mITT)		SAE (any)		SAE (drug-related)	
	aOR (95% CI)*	*P* value	aOR (95% CI)*	*P* value	aOR (95% CI)*	*P* value
Rifampicin dosage (for every increase with 10 mg R/kg)	0.68 (0.41–1.11)	0.12	0.83 (0.40–1.79)	0.63	1.20 (0.43–3.31)	0.73
HZE dosage (for every increase with 10 mg HZE/kg)	0.97 (0.70–1.35)	0.87	1.77 (1.06–2.97)†	0.03†	1.91 (1.05–3.51)†	0.04†

* Adjusted for hospital, new/retreatment case, HZE dosage (the sum of H, Z and E dose in mg divided by the patient's weight in kg) and body weight category (33–41 kg vs. other).
† Statistically significant.
mITT = modified intention-to-treat; aOR = adjusted odds ratio; CI = confidence interval; SAE = serious adverse event; R = rifampicin; H = isoniazid, Z = pyrazinamide, E = ethambutol.

Table 4 Drug-related SAEs during treatment

	Intervention		Control		
	n	(%)	*n*	(%)	aOR[#]
Total*	(*n* = 352)		(*n* = 349)		
Any SAE	9	(2.6)	15	(4.3)	0.58 (0.24–1.33)
Vomiting	0		2	(0.6)	
Ataxia/peripheral neuritis	0		1	(0.3)	
Asymptomatic, ALT >5x ULN	2	(0.6)	5	(1.4)	
Hepatitis/jaundice	6	(1.7)	6	(1.7)	
Any grade 3–4 transaminase increase[†‡]	3	(0.9)	7	(2.0)	
Weight <33 or >41 kg[§]	(*n* = 212)		(*n* = 193)		
Any SAE	6	(2.8)	5	(2.6)	1.06 (0.31–3.75)
Vomiting	0	(0.0)	2	(1.0)	
Ataxia/peripheral neuritis	0		0		
Asymptomatic, ALT >5x ULN	2	(0.9)	2	(1.0)	
Hepatitis/jaundice	4	(1.9)	1	(0.5)	
Any grade 3–4 transaminase increase[†‡]	3	(1.4)	3	(1.6)	0.81 (0.16–4.09)
Weight band 33-41 kg[§]	(*n* = 140)		(*n* = 156)		
Any SAE	3	(2.1)	10	(6.4)	0.28 (0.06–0.97)[¶]
Vomiting	0		0		
Ataxia/peripheral neuritis	0		1	(0.6)	
Asymptomatic, ALT >5x ULN	0		3	(1.9)	
Hepatitis/jaundice	2	(1.4)	5	(3.2)	
Any grade 3–4 transaminase increase[†‡]	0	(0.0)	4	(2.6)	0.33 (0.03–1.03)

* Safety analysis includes all patients who received at least a single dose, and according to the regimen actually received.
† Not only drug-related.
‡ Proportions calculated excluding those with 1) missing values, or 2) baseline-increased ALT.
§ Due to an erroneous bench aid used in the study clinics, patients in the 33–41 kg weight band of the intervention arm was given only 2/3 of the HZE dose given to the same weight band in the control arm.
# Adjusted for hospital.
¶ Statistically significant.
SAE = serious adverse event; aOR = adjusted odds ratio; ULN = upper limit of normal; ALT = alanine aminotransferase; H = isoniazid; Z = pyrazinamide; E = ethambutol.

An accidental finding was the significant correlation between drug-related SAE and increase in HZE dosage and the lower occurrence of drug-related SAE in the RMP double-dosed/HZE under-dosed intervention subgroup. Moreover, the estimated occurrence of hepatic SAE in the RMP double-dosed/HZE underdosed intervention subgroup (weight 33–41 kg) was lower than in the control group, but this difference was not significant ($P = 0.09$). These findings might point to PZA or INH but not RMP—even at double-dose—as the most hepatotoxic drug in first-line TB treatment. The combined toxicity of RMP with PZA has long been known to be higher than for RMP plus INH,[19] and was described as severe and even fatal with high-dose PZA.[20,21]

In 2011, a systematic review concluded that daily high-dose RMP of up to 15 mg/kg was safe.[22] Additional to this, our trial indicates that a dose of up to 20 mg/kg is safe when used during 6 months in a programmatic setting. Additional trials are needed to assess if even higher dosages (up to 35 mg/kg), are shown to be safe in a small cohort during a few months of treatment,[8] can also be used safely during the entire 6 months of first-line treatment. A recent study has recommended the use of high-dose RMP in patients at risk of an unfavourable treatment outcome.[23]

Our study did not show a significant increase in efficacy among patients treated with double-dose RMP. This may be explained by the large number of patients excluded from the analysis. Moreover, bacteriologically defined recurrences were few overall, particularly smear- and/or culture-defined relapses, which may be explained by the low prevalence of resistance to first-line drugs.[24] However, a protective effect of double-dose RMP is not excluded by our findings. The width of the 95% CI (aOR 0.68, for every increase with 10 mg R/kg; 95%CI 0.41–1.11; $P = 0.12$) shows that a large effect of double dose on efficacy is not excluded, and might be identified by a larger study with more power, or in a study population with a higher mortality and/or occurrence of failure/relapse. Future trials may confirm if drug-related toxicity can be reduced by combining high-dose RMP with a lower dose of the other first-line drugs. If safe and efficacious, future trials should also assess if higher dosages (up to 35 mg/kg, possibly combined with a shorter treatment duration) not only increase the conversion rate,[8] but also increase the probability of relapse-free treatment success, which is the ultimate goal of TB treatment.

CONCLUSIONS

In this relatively large number of patients, double- and standard dose RMP-based first-line treatment regimens were not statistically significantly different in terms of occurrence of unfavourable outcomes and

safety. Smaller studies have shown that the bactericidal activity of RMP increases further with still higher doses. Because safety does not seem to be dose-dependent, larger trials with more power, or trials with at least triple-dose might be needed to clearly see the effect of high-dose RMP on unfavourable outcomes. Erroneous HZE under-dosing of a subgroup with double-dose RMP did not result in poorer outcomes, but did reduce the occurrence of hepatotoxicity.

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References

1 Van Deun A, Decroo T, Piubello A, de Jong B C, Lynen L, Rieder H L. Principles for constructing a tuberculosis treatment regimen: the role and definition of core and companion drugs. (Perspective). Int J Tuberc Lung Dis 2018; 22: 239–245.
2 Jindani A, Aber V R, Edwards E A, Mitchison D A. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis 1980; 121: 939–949.
3 Fox W, Ellard G A, Mitchison D A. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946-1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999; 3(Suppl 2): S231–S279.
4 World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017 update. WHO/HTM/TB/2017.05. Geneva, Switzerland: WHO, 2017.
5 van Ingen J, Aarnoutse R E, Donald P R, et al. Why do we use 600 mg of rifampicin in tuberculosis treatment? (Viewpoint) Clin Infect Dis 2011; 52: e194–e199.
6 Verbist L. European Symposium - rifampicin, 10–11 March 1969. Rifampicin activity "in vitro" and in established tuberculosis in mice. Acta Tuberc Pneumol Belg 1969; 60: 397–412.
7 Mitchison D A. Pharmacokinetic/pharmacodynamic parameters and the choice of high-dosage rifamycins. Int J Tuberc Lung Dis 2012; 16: 1186–1189.
8 Boeree M J, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. Lancet Infect Dis 2017; 17: 39–49.
9 Seijger C, Hoefsloot W, Bergsma-de Guchteneire I, et al. High-dose rifampicin in tuberculosis: experiences from a Dutch tuberculosis centre. PLoS One 2019; 14: e0213718.
10 Boeree M J, Diacon A H, Dawson R, et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. Am J Respir Crit Care Med 2015; 191: 1058–1065.
11 Jindani A, Borgulya G, Westermann de Patiño I, et al. A randomised Phase II trial to evaluate the toxicity of high-dose rifampicin to treat pulmonary tuberculosis. Int J Tuberc Lung Dis 2016; 20: 832–838.
12 Alam M S, Sarker M S, Mahmud A M, et al. Low HIV infection rates among tuberculosis patients in Dhaka, Bangladesh. Int J STD AIDS 2005; 16: 86–88.
13 Stop TB Partnership - Global Laboratory Initiative Working Group. The handbook: laboratory diagnosis of tuberculosis by sputum microscopy. Global edition. Adelaide, Australia: SA Pathology, 2013.
14 Canetti G, Fox W, Khomenko A, Mitchison D A, Rist N, Smelev N A. Advances in techniques of testing mycobacterial drug sensitivity, and the use of sensitivity tests in tuberculosis control programmes. Bull World Health Organ 1969; 41: 21–43.
15 Ng K C S, Supply P, Cobelens F G J, et al. How well do routine molecular diagnostics detect rifampicin heteroresistance in *Mycobacterium tuberculosis*? J Clin Microbiol 2019; 57(11): e00717–19.
16 World Health Organization. Treatment of tuberculosis: guidelines for national programmes. 4th ed. WHO/HTM/TB/2009.420. Geneva, Switzerland: WHO, 2010.
17 International Council for Harmonization of technical requirements for pharmaceuticals for human use (ICH). ICH harmonized guideline. Integrated addendum to ICH E6 (R1). Guideline for good clinical practice E6(R2). Current Step 4 version. Geneva, Switzerland: ICH, 2016.
18 Wilson E B. Probable inference, the law of succession, and statistical inference. J Am Stat Assoc 1927; 22: 209–212.
19 Centers for Disease Control and Prevention. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revision in American Thoracic Society/CDC recommendations—United States, 2001. Morb Mortal Wkly Rep 2001; 50: 733–735.
20 Teleman M D, Chee C B E, Earnest A, Wang Y T. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis 2002; 6: 699–705.
21 Mount F W, Wunderlich G S, Murray S J, Ferebee S H. Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. A United States Public Health Service tuberculosis therapy trial. Am Rev Respir Dis 1959; 80: 371–387.
22 Steingart K R, Jotblad S, Robsky K, et al. Higher-dose rifampin for the treatment of pulmonary tuberculosis: a systematic review. Int J Tuberc Lung Dis 2011; 15: 305–316.
23 Seijger C, Hoefsloot W, Bergsma-de Guchteneire I, et al. High-dose rifampicin in tuberculosis: experiences from a Dutch tuberculosis centre. PLoS One 2019; 14: e0213718.
24 Van Deun A, Aung K J M, Hossain M A, et al. Twenty years of rifampicin resistance surveillance in Bangladesh: periodic vs. continuous monitoring. Int J Tuberc Lung Dis 2018; 22: 1450–1461.

RÉSUMÉ

OBJECTIF : Comparer la survenue de résultats défavorables en termes de traitement et de sécurité d'une double dose (20 mg/kg/j, intervention) par rapport à la dose standard (10 mg/kg/j, témoin) de rifampicine (RMP) dans un protocole de traitement de première ligne de la tuberculose (TB) pour des patients TB à frottis positif au Bangladesh.

SCHÉMA : Ceci était un essai clinique randomisé. Les paramètres principaux en termes d'efficacité et de sécurité ont été la survenue d'un résultat défavorable du traitement (décès, échec, rechute ou perte de vue) et la survenue d'un quelconque effet secondaire grave du médicament (SAE).

RÉSULTATS : Dans l'analyse d'efficacité primaire, parmi 343 témoins et 347 patients de l'intervention, 15,5% et 11,8% ont respectivement eu un résultat défavorable. Dans l'analyse de sécurité, parmi 349 patients de l'intervention et 352 témoins, 4,3% et 2,6% ont subi des effets secondaires graves liés au traitement. Ces différences n'ont pas été significatives. La survenue d'effets secondaires graves a été significativement plus faible, ce qui s'explique par une moindre toxicité hépatique, dans un sous-groupe recevant de la rifampicine à double dose et un sous-dosage de HZE (isoniazide+pyrazinamide+éthambutol) par erreur.

CONCLUSION : Nos résultats ne montrent pas de différence statistiquement significative en terme d'efficacité et de sécurité entre dose standard et double dose de RMP. Un résultat imprévu suggère que la RMP à haute dose est une moindre cause d'hépatotoxicité. Des essais plus vastes avec davantage de puissance ou des essais avec au moins une triple dose seraient nécessaires pour voir clairement l'effet de la RMP à haute dose sur les résultats défavorables.

RESUMEN

OBJETIVO: Comparar la frecuencia de resultados terapéuticos desfavorables y de seguridad de una dosis doble de rifampicina (RMP) (20 mg/kg diarios, intervención) y la dosis corriente (10 mg/kg diarios, testigo), en un esquema antituberculoso de primera línea para pacientes con tuberculosis (TB) y baciloscopia positiva de Bangladesh.

MÉTODO: Fue este un ensayo clínico aleatorizado. Los principales criterios de valoración de eficacia y seguridad fueron la presencia de un desenlace terapéutico desfavorable (muerte, fracaso, recaída o pérdida durante el seguimiento) y la aparición de cualquier reacción adversa grave a los medicamentos.

RESULTADOS: Según el análisis primario de eficacia, en 343 pacientes testigo y 347 del grupo de intervención se observaron desenlaces desfavorables en 11,8% y 15,5% respectivamente. En el análisis de seguridad, de 349 pacientes de la intervención y 352 del grupo testigo se presentaron reacciones adversas graves en 4,3% y 2,6%, respectivamente. Estas diferencias no alcanzaron significación estadística. La aparición de reacciones adversas graves fue notablemente menor, debido a menos casos de hepatotoxicidad en un subgrupo de pacientes que por error recibió dosis doble de RMP, pero una posología subterapéutica de HZE (isoniazida+pirazinamida+etambutol).

CONCLUSIÓN: Estos resultados no demuestran una diferencia significativa entre la dosis corriente y la dosis doble de RMP con respecto a la eficacia y la seguridad. Una observación accidental indica que la dosis alta de RMP es una causa menor de hepatotoxicidad. Serían necesarios ensayos clínicos más grandes con mayor potencia estadística con el fin de esclarecer el efecto de la dosis alta de RMP en los desenlaces desfavorables.