Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial

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Summary

Background Intensified antibiotic treatment might improve the outcome of tuberculous meningitis. We assessed pharmacokinetics, safety, and survival benefit of several treatment regimens containing high-dose rifampicin and moxifloxacin in patients with tuberculous meningitis in a hospital setting.

Methods In an open-label, phase 2 trial with a factorial design in one hospital in Indonesia, patients (aged >14 years) with tuberculous meningitis were randomly assigned to receive, according to a computer-generated schedule, first rifampicin standard dose (450 mg, about 10 mg/kg) orally or high dose (600 mg, about 13 mg/kg) intravenously, and second oral moxifloxacin 400 mg, moxifloxacin 800 mg, or ethambutol 750 mg once daily. All patients were given standard-dose isoniazid, pyrazinamide, and adjunctive corticosteroids. After 14 days of treatment all patients continued with standard treatment for tuberculosis. Endpoints included pharmacokinetic analyses of the blood and cerebrospinal fluid, adverse events attributable to tuberculosis treatment, and survival. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01158755.

Findings 60 patients were randomly assigned to receive rifampicin standard dose (12 no moxifloxacin, ten moxifloxacin 400 mg, and nine moxifloxacin 800 mg) and high dose (ten no moxifloxacin, nine moxifloxacin 400 mg, and ten moxifloxacin 800 mg). A 33% higher dose of rifampicin, intravenously, led to a three times higher geometric mean area under the time-concentration curve up to 6 h after dose (AUC_{0-6}; 78·7 mg.h/L [95% CI 71·0–87·3] vs 26·0 mg.h/L [19·0–35·6]), maximum plasma concentrations (C_{max}; 22·1 mg/L [19·9–24·6] vs 6·3 mg/L [4·9–8·3]), and concentrations in cerebrospinal fluid (0·60 mg/L [0·46–0·78] vs 0·21 mg/L [0·16–0·27]). Doubling the dose of moxifloxacin resulted in a proportional increase in plasma AUC_{0-6} (31·5 mg.h/L [24·1–41·1] vs 15·1 mg.h/L [12·8–17·7]), C_{max} (7·4 mg/L [5·6–9·6] vs 3·9 mg/L [3·2–4·8]), and drug concentrations in the cerebrospinal fluid (2·43 mg/L [1·81–3·27] vs 1·52 mg/L [1·28–1·82]). Intensified treatment did not result in increased toxicity. 6 month mortality was substantially lower in patients given high-dose rifampicin intravenously (ten [35%] vs 20 [65%]), which could not be explained by HIV status or severity of disease at the time of presentation (adjusted HR 0·42; 95% CI 0·20–0·91; p=0·03).

Interpretation These data suggest that treatment containing a higher dose of rifampicin and standard-dose or high-dose moxifloxacin during the first 2 weeks is safe in patients with tuberculous meningitis, and that high-dose intravenous rifampicin could be associated with a survival benefit in patients with severe disease.

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Introduction

Meningitis is the most severe form of tuberculosis, resulting in death or neurological disability in 50% of patients.[1,2] The treatment in patients with tuberculous meningitis follows the model for short-course chemotherapy in patients with pulmonary tuberculosis, but the optimum drug regimen and duration have not been established.

Rifampicin is important in the treatment of tuberculous meningitis as shown by the high mortality in patients with rifampicin-resistant tuberculous meningitis.[3,4] However, the dose used is at the low end of the dose-response curve,[5,6] and the penetration of rifampicin into cerebrospinal fluid is low.[7] Higher doses of rifampicin for

pulmonary tuberculosis have been assessed in several clinical trials reported before 1985.[8,9] Until now, no data were available for the use of high-dose rifampicin in tuberculous meningitis, although one clinical trial is underway in Vietnam.[10] Apart from a higher dose of rifampicin, intravenous rather than oral administration might improve the drug penetration into the plasma and cerebrospinal fluid.

Penetration of other standard drugs for tuberculosis, isoniazid and pyrazinamide, into the cerebrospinal fluid is good and they are important for treatment of tuberculous meningitis. By contrast, neither ethambutol nor streptomycin, both commonly used drugs, show good penetration into the cerebrospinal fluid in the

absence of inflammation. Fluoroquinolones might be good alternatives to these drugs. Of the fluoroquinolones, moxifloxacin has the highest activity against *Mycobacterium tuberculosis* in vitro and in mice.[11,12] The combination of rifampicin and moxifloxacin has been assessed in clinical trials with the aim of shortening the treatment in patients with tuberculosis.[13–15] Moxifloxacin has a good penetration in cerebrospinal fluid[16] and in patients with tuberculous meningitis.[17] Of note, data from in-vitro studies and those in animals suggest that the optimum dose of moxifloxacin for tuberculosis could be higher than the standard dose of 400 mg once daily[18,19] particularly because rifampicin lowers the plasma concentrations of moxifloxacin by about 30%.[20]

Therefore, in view of the high morbidity and mortality associated with tuberculous meningitis, we have assessed intensified treatment regimens containing high-dose rifampicin and moxifloxacin.

Methods

Study design

This study was an open-label, randomised, phase 2, clinical trial with a factorial design. It was done at Hasan Sadikin Hospital, Bandung, Indonesia—the referral hospital for West Java province (population 43 million). High-dose rifampicin and standard-dose or high-dose moxifloxacin were assessed as part of a four-drug regimen for tuberculous meningitis. Patients were given intensified regimens for the first 2 weeks of treatment and then all patients were given standard treatment. Most deaths occur during the first few weeks, and longer intravenous treatment would be difficult because most patients who survive the initial stage return home after 2 weeks of hospital admission.

The primary objectives were to assess the pharmacokinetics and safety or tolerability of the intensified treatment regimens. Secondary objectives were to compare neurological response and mortality in patients with tuberculous meningitis given intensified or standard treatment.

The study was approved by the ethical review board of Hasan Sadikin Hospital and Medical Faculty of Universitas Padjadjaran, Bandung, Indonesia, and the ethical committee of Radboud University, Nijmegen, Netherlands. Compliance with the study protocol was assessed by internal monitoring and two external audits. Written informed consent for participation in the trial, and rapid HIV testing, was obtained from patients or close relatives of patients who were unconscious.

Patients

All patients older than 14 years admitted with clinically suspected meningitis between October, 2010, and December, 2011, had an initial screening that included standard cerebrospinal fluid and blood tests, and chest radiography. In Indonesia, neuroradiology is rarely done in patients in this setting and is not covered by government health insurance for the poor.

Microbiological testing included microscopy for cryptococci, acid-fast bacilli, and bacterial pathogens in the cerebrospinal fluid; culture for *M tuberculosis*, bacterial pathogens, and fungi; cryptococcal antigen testing; and *M tuberculosis* drug-resistance testing with proportional methods.

CD4-cell testing and antiretroviral treatment were available for individuals who tested positive for HIV. Hepatitis C virus antibodies and hepatitis B virus surface antigen were also tested, and a 12-lead electrocardiogram (ECG) was done to check for possible ECG abnormalities, including prolonged QTc (>0·42 s for male and >0·45 s for female patients).

All patients with definite, probable, or possible tuberculous meningitis[21] were eligible for the study. Exclusion criteria were failure to do a diagnostic lumbar puncture or evidence of bacterial or cryptococcal meningitis. Other exclusion criteria were treatment for tuberculosis for more than 7 days before admission, a history of tuberculous meningitis, pregnancy, lactation, a known contraindication to moxifloxacin, alanine aminotransferase activity more than five times the upper limit of normal, known hypersensitivity or intolerance to rifampicin or moxifloxacin, rapid clinical deterioration (eg, signs of sepsis, decreasing consciousness or signs of cerebral oedema, or herniation) during the screening process, and no informed consent. The neurological status of patients was classified according to a modification of the British Medical Research Council (BMRC) grading system as 1 (Glasgow Coma Scale [GCS] 15 with no focal neurological signs), 2 (GCS 11–14 or 15 with focal neurological signs), or 3 (GCS <10).[22]

Randomisation and masking

An independent person, not involved in patient care, computer generated the randomisation list. None of the physicians or investigators had access to this list. Investigators, notified by treating physicians, enrolled patients meeting the inclusion criteria into the study. Patients were randomly assigned to one of six groups after stratification for HIV infection as the strongest risk factor for death in tuberculous meningitis.[1] In accordance with the factorial design, patients were first randomly assigned to receive a regimen with rifampicin at a standard dose (450 mg once daily, about 10 mg/kg, orally) or high dose (600 mg once daily, about 13 mg/kg, intravenously). The patients were then randomly assigned to receive oral ethambutol (750 mg), standard-dose moxifloxacin (400 mg), or high-dose moxifloxacin (800 mg). All patients were given oral isoniazid (300 mg/day), pyrazinamide (1500 mg/day), and pyridoxine (50 mg/day). The fixed dosing of standard first-line drugs for tuberculosis (irrespective of weight) was in accordance with prevailing practice. The allocated treatment regimen was not masked from doctors, nurses, and patients because intravenous and oral routes of rifampicin were compared.

Treatment

After 14 days, all patients continued taking the standard regimen, consisting of oral isoniazid 300 mg/day, rifampicin 450 mg/day, pyrazinamide 1500 mg/day, and ethambutol 750 mg/day for 2 months, with subsequent rifampicin 450 mg/day and isoniazid 300 mg/day for 4 months in accordance with the Indonesian National Tuberculosis Program. All participants were given adjunctive dexamethasone intravenously for the first 6–8 weeks, starting with 0·4 mg/kg for grade 2 or 3, and 0·3 mg/kg for grade 1 tuberculous meningitis, with dose reduction as described previously.[22] Patients with both tuberculous meningitis and newly diagnosed HIV infection were started on antiretroviral treatment 4–8 weeks after the start of treatment.[23]

For the intervention groups, intravenous rifampicin (Rifadin, Sanofi Aventis, Gouda, Netherlands) and moxifloxacin 400 mg tablets (Avelox, Bayer, Jakarta, Indonesia) were used. Government-approved standard treatment consisted of oral rifampicin, isoniazid, pyrazinamide, and ethambutol (Ethambutol, PT Kimia Farma, Bandung, Indonesia). These drug formulations had previously been assessed in this setting,[8] and the Indonesian rifampicin formulation had shown bioavailability equal to the international reference.[24] All oral drugs were given once daily on an empty stomach. For unconscious patients who could not swallow, drugs were dissolved in 30 mL plain water in a closed syringe and delivered through a nasogastric tube, which was then flushed. For a more reliable route of administration in the intensified regimen, 600 mg of rifampicin was diluted in 250 mL of normal saline infusion (0·9% sodium chloride) and given over 90 min. During the first 2 weeks of treatment, facility-based directly observed treatment was used by the physicians or nurses to administer the drugs. Intake of drug was checked with the hand-and-mouth procedure. After these 2 weeks, adherence was monitored by pill count every 2–4 weeks.

Pharmacokinetic assessment

Pharmacokinetic sampling was done in the first 3 days of drug administration. Serial blood sampling was done just before and at 1 h, 2 h, 4 h, 6 h, and 24 h after dosing as previously described.[8] Two samples of cerebrospinal fluid were taken on the same day as the blood samples and more than 24 h after the first sampling of cerebrospinal fluid, between 3 h and 6 h and starting from 6 h until 9 h after drug administration, respectively.

The total (protein-bound plus unbound) plasma and cerebrospinal concentrations of rifampicin and moxifloxacin were assessed at Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, using high performance liquid chromatography assays that were validated and that performed well in an international quality control programme.[8,20] For rifampicin, accuracy for standard concentrations was between 99·8% and 100·4% dependent on the concentration. The intra-assay

and inter-assay coefficients of variation were less than 4% for a concentration of 0·26–30 mg/L. The lower limit of quantification was 0·26 mg/L. For moxifloxacin, accuracy was greater than 95% at all standard concentrations. Intra-assay and inter-assay coefficients were from 1·4% to 5·4% and 0·2% to 3·9%, respectively. The lower limit of quantification was 0·03 mg/L.

Pharmacokinetic parameters for rifampicin and moxifloxacin in plasma were assessed non-compartmentally with WinnonLin Professional (version 5.0). The highest plasma concentrations were defined as C_{max}, with the corresponding times as T_{max}. The area under the time-concentration curve up to 6 h after dose (AUC_{0-6}) and up to 24 h after dose in plasma were calculated with the log-linear trapezoidal rule from zero up to 6 h and 24 h, respectively. If the concentration at 24 h after dose (C_{24}) was less than the limit of quantification, it was calculated with the formula,

$$C_{24} = C_{last} \times e^{-\beta \times (24 - T_{last})}$$

in which C_{last} is the last measurable concentration at T_{last} and β is the first-order elimination rate constant. β was obtained with least squares linear regression analysis on log C versus time, with the absolute slope of the regression line being $\beta/2\cdot303$. If β could not be estimated (in view of the sampling only being done up to 6 h after dose), only AUC_{0-6} was assessed. C_{max} in the cerebrospinal fluid was estimated as the highest concentration measured in the intervals of 3–6 h and 6–9 h after dose.

Follow-up

Patients were followed up until 6 months after the start of treatment. In the first 2 weeks of treatment, the tuberculous meningitis and possible drug-related adverse events were monitored daily, with twice weekly ECG, full blood count, and liver transaminases. More frequent or other investigations were done as clinically indicated. After discharge, patients were reviewed monthly.

Because of the severity of tuberculous meningitis, with a 6 month mortality of 47% in our previous series,[1] adverse events were defined as those possibly or probably related to treatment (ie, hepatotoxicity, cardiotoxicity, hypersensitivity, and haematological changes). All other adverse events (eg, new neurological signs and respiratory failure) were not incorporated in the assessment of safety and toxicity. Classification of adverse events was based on the US National Institutes of Health Common Terminology Criteria for Adverse Events (version 4.0). The various grades of toxicity were managed in accordance with our predetermined toxicity management guidelines; treatment was stopped in patients who had grade 4 toxicity.

Survival was monitored during hospital admission, and afterwards through social workers for patients who did not attend scheduled appointments. The cause of death was ascertained with clinical and laboratory assessments,

For the **Common Terminology Criteria for Adverse Events** see http://evs.nci.nih.gov/ftp1/CTCAE

and classified as neurological, non-neurological, or uncertain. No post mortem was done.

Statistical analysis

Because this study was exploratory, no sample size calculation was done, but subgroups of 20 (moxifloxacin) and 30 patients (rifampicin) were judged to be sufficient to assess safety and pharmacokinetics of intensified versus standard treatment for tuberculous meningitis. Patients' characteristics, and pharmacokinetic and safety or tolerability data were presented descriptively for each group. Differences in pharmacokinetic parameters between study groups were not tested. Groups were pooled to present pharmacokinetic data for rifampicin dose (three groups combined), or moxifloxacin dose (two groups combined) if descriptive analysis suggested differences no larger than 25% in geometric mean AUC or C_{max} values between groups. Differences in pharma-cokinetic parameters were tested with the independent samples t test on logarithmically transformed values of AUC and C_{max}. T_{max} values were compared with the Wilcoxon rank-sum test. The χ^2 test was used to compare proportions of patients with rifampicin peak plasma concentrations within the reference range of 8–24 mg/L.[25] Data for safety or tolerability and survival were analysed in accordance with the intention-to-treat principle. χ^2 tests were also used for comparison of proportions of patients with adverse events. A Cox regression analysis was used to assess the effects of rifampicin dose, moxifloxacin use and dose, HIV status, rifampicin resistance, and GCS at the time of treatment initiation on survival in all patients, and in those with culture-confirmed tuberculous meningitis. All analyses were planned and no post-hoc analysis was done. All statistical analyses were done with SPSS (version 18.0.2) for Windows. p values of less than 0·05 were judged significant in all analyses.

This trial is registered with ClinicalTrials.gov, number NCT01158755.
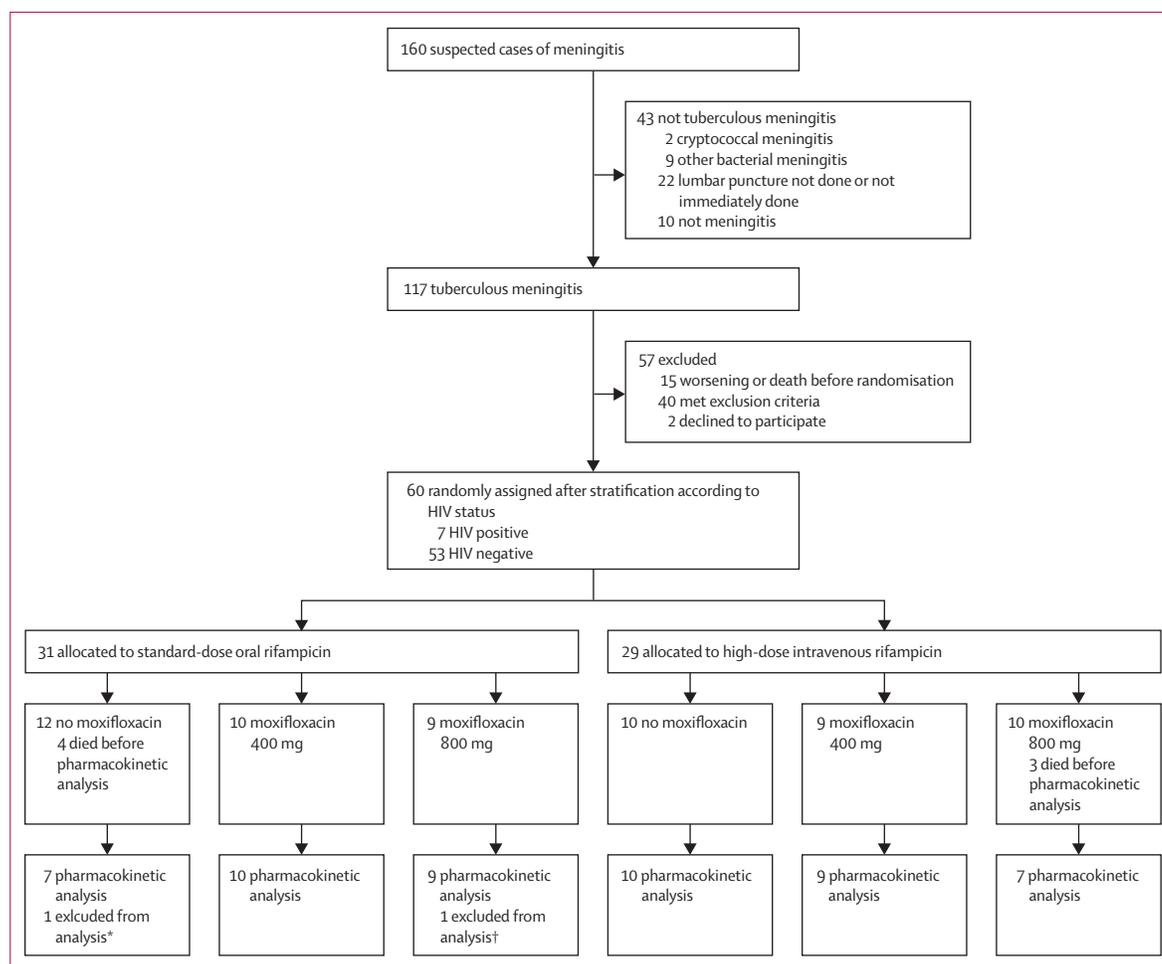

Figure 1: **Trial profile**

All patients received oral isoniazid and pyrazinamide, and intravenous dexamethasone. *Patient excluded because of unreliable bioanalysis result. †Patient excluded from pharmacokinetic assessments of rifampicin only; 52 patients had pharmacokinetic assessments of rifampicin and 35 had pharmacokinetic assessments of moxifloxacin.

	All patients (n=60)	Oral rifampicin 450 mg (n=31)			Intravenous rifampicin 600 mg (n=29)		
		No moxifloxacin (n=12)	Moxifloxacin 400 mg (n=10)	Moxifloxacin 800 mg (n=9)	No moxifloxacin (n=10)	Moxifloxacin 400 mg (n=9)	Moxifloxacin 800 mg (n=10)
Sex, male	33 (55%)	8 (67%)	6 (60%)	4 (44%)	4 (40%)	3 (33%)	8 (80%)
Age (years)	28 (16–64)	34 (19–47)	33 (19–50)	27 (18–57)	29 (16–49)	27 (18–60)	27 (19–64)
Bodyweight (kg)	48 (34–75)	50 (35–57)	49 (40–55)	48 (40–58)	46 (34–54)	47 (42–62)	49 (40–75)
Body-mass index (kg/m²)	18·4 (15·1–26·0)	18·0 (16·0–23·3)	18·6 (15·6–22·9)	18·3 (15·4–23·3)	18·1 (15·1–21·6)	18·4 (16·3–24·7)	19·9 (16·5–26·0)
Tuberculous meningitis (grade)							
1	4 (7%)	0	0	1 (11%)	2 (20%)	1 (11%)	0
2	49 (82%)	12 (100%)	10 (100%)	5 (56%)	7 (70%)	7 (78%)	8 (80%)
3	7 (12%)	0	0	3 (33%)	1 (10%)	1 (11%)	2 (20%)
Infected with HIV	7 (12%)	2 (17%)	1 (10%)	1 (11%)	1 (10%)	1 (11%)	1 (10%)
Glasgow Coma Scale <14 on presentation	46 (77%)	11 (92%)	8 (80%)	8 (89%)	5 (50%)	5 (56%)	9 (90%)
Drug dose (mg/kg)							
Rifampicin (n=60)	10·8 (7·8–17·6)	9·0 (7·9–12·9)	9·2 (8·2–11·3)	9·4 (7·8–11·3)	13·1 (11·2–17·6)	12·8 (10·0–14·3)	12·2 (8·0–15·0)
Isoniazid (n=60)	6·3 (4·0–8·8)	6·0 (5·3–8·6)	6·2 (5·5–7·5)	6·3 (5·2–7·5)	6·5 (5·6–8·8)	6·4 (5·0–35·7)	6·1 (4·0–7·5)
Pyrazinamide (n=60)	31·3 (20·0–44·1)	30·0 (26·3–42·9)	30·6 (27·3–37·5)	31·2 (25·9–37·5)	32·6 (27·8–44·1)	31·9 (25·0–35·7)	30·6 (20·0–37·5)
Ethambutol (n=22)	15·6 (13·2–22·1)	15·0 (13·2–21·4)	..	..	16·3 (13·9–22·1)	..	..
Moxifloxacin (n=38)	10·3 (6·7–20·0)	..	8·2 (7·3–10·0)	16·7 (13·8–20·0)	..	8·5 (6·7–9·5)	16·3 (10·7–20·0)
Initial oral treatment through nasogastric tube	46 (77%)	11 (92%)	8 (80%)	8 (89%)	5 (50%)	5 (56%)	9 (90%)

Data are number (%) or median (range).

Table 1: **Patients' characteristics and drug doses**

Role of the funding source

The funders of the study had no role in the study design, data gathering, analysis, or interpretation of the results, and writing of the report. All authors had full access to the data. The corresponding author had the final responsibility for the decision to submit the report for publication.

Results

60 of 160 suspected cases of meningitis screened between October, 2010, and December, 2011, were randomly assigned to receive standard-dose or high-dose rifampicin (figure 1). Informed consent was obtained from close relatives of 46 patients who were unconscious at presentation. Table 1 shows the baseline characteristics of patients randomly assigned to receive the two doses of rifampicin. 55% of patients were men (table 1); median duration of symptoms before presentation was 14 days (IQR 7–21). 12% of patients had an HIV infection (table 1). The six groups were not equally balanced in terms of age and sex (table 1). Symptoms at presentation included reduced consciousness (47 [78%]), headache (58 [97%]), seizures (four [7%]), weight loss (42 [70%]), and cough (34 [57%]). Six patients (10%) reported previous treatment for tuberculosis. On physical examination, lowered consciousness was noted in 47 patients (78%; median GCS 13, range 8–15). Neck stiffness (57 [95%]), cranial nerve palsies (23 [38%]), and motor deficit, most commonly hemiparesis (30 [50%]),

	600 mg, intravenous (n=26)	450 mg, oral (n=26)	Ratio of intravenous to oral	p value
Plasma				
AUC_{0-6} (mg.h/L)	78·7 (71·0–87·3)	26·0 (19·0–35·6)	3·0 (2·2–4·2)	<0·0001*
C_{max} (mg/L)	22·1 (19·9–24·6)	6·3 (4·9–8·3)	3·5 (2·6–4·8)	<0·0001*
C_{max} (≥8 mg/L)	26 (100%)	13 (50%)	..	<0·0001†
T_{max} (h; median, range)	2 (1– 2)	2 (1–6)	..	0·048‡
CSF				
C_{max} (mg/L)§	0·60 (0·46–0·78)	0·21 (0·16–0·27)	2·92 (2·03–4·20)	<0·0001*

Data are number (%) or geometric mean (95% CI), unless otherwise indicated. Rifampicin concentrations were measured for plasma AUC_{0-6} and CSF C_{max} in samples obtained during the first 3 days of treatment. Assessment of plasma AUC_{0-24} values was difficult in 41 patients because rifampicin concentrations at C_{24} were below the limit of quantification. Estimation of the C_{24} based on the last measurable concentration and the elimination rate constant was not possible because the elimination rate for rifampicin could not be assessed reliably with sampling at 2 h, 4 h, and 6 h after dose. For this reason, only AUC_{0-6} is shown. AUC_{0-6}=area under the time-concentration curve up to 6 h after dose. AUC_{0-24}=area under the time-concentration curve up to 24 h after dose. C_{max}=maximum plasma concentration. T_{max}=time to C_{max}. CSF=cerebrospinal fluid. C_{24}=rifampicin concentration at 24 h after dose. *Independent-samples t test after log transformation. †χ^2 test. ‡Wilcoxon rank-sum test. §CSF samples were obtained from 25 patients on 600 mg intravenous and 25 patients on 450 mg oral rifampicin; in one and 16 patients, respectively, rifampicin, concentrations in CSF were below the limit of quantification of the assay (0·26 mg/L) and were set at half the limit of quantification (0·13 mg/L) to enable comparison of exposures in CSF.

Table 2: **Pharmacokinetic data for rifampicin (n=52)**

were also noted. Most patients presented with BMRC grade 2 (49 [82%]) or grade 3 (seven [12%]) tuberculous meningitis. Chest radiography suggested pulmonary tuberculosis in 28 patients (47%), based on infiltrative (n=21), miliary (n=6), and cavitary (n=1) lesions.

Consistent with a diagnosis of tuberculous meningitis, cerebrospinal fluid showed pleocytosis with a

predominance of lymphocytes (median 96 cells per µL [IQR 29–260]; 80% mononuclear cells [43–90]), a low ratio of cerebrospinal fluid to blood glucose (0·28 [0·11–0·41]), and raised protein concentration (1660 mg/L [1000–3130]).

Tuberculous meningitis was bacteriologically confirmed in 31 patients (52%), based on a combination of culture (n=29) and microscopy (n=9). With the clinical scoring system,[21] 20 remaining patients (33%) had probable tuberculous meningitis, whereas the other nine (15%) had possible tuberculous meningitis. Bacterial and cryptococcal meningitis was excluded in all patients.

Seven patients died before the pharmacokinetic sampling was done (figure 1). For 22 patients, sampling was done 1 day after the start of treatment. For logistical reasons (eg, weekends and heavy patient loads), sampling was done on day 2 in 20 patients and on day 3 in 11.

In view of the short duration of sampling, up to 6 h after rifampicin dosing, assessment of plasma AUC_{0-24} was difficult in most patients. Geometric mean AUC_{0-6} and C_{max} for rifampicin in plasma were at least three times higher in patients given a high dose intravenously (table 2). Five (19%) of 26 patients taking oral rifampicin at the standard dose (450 mg) had low C_{max} (<4 mg/L) compared with none of the 26 given a high dose intravenously. Standard dose oral rifampicin resulted in low concentrations in the cerebrospinal fluid (table 2). At least one sample of cerebrospinal fluid was available for 25 patients on standard dose rifampicin; in 16 of these patients (64%), rifampicin concentrations in cerebrospinal fluid were below the assay limit of quantification (0·26 mg/L). By contrast, rifampicin concentrations in the cerebrospinal fluid were below the limit of quantification in one (4%) of 25 patients on high-dose intravenous rifampicin. Administration of the high dose increased rifampicin concentrations by almost three times in the cerebrospinal fluid (table 2).

For moxifloxacin, plasma AUC_{0-24} could be reliably assessed in 24 of 35 patients; in the other 11 patients, plasma concentrations were still increasing at 6 h. Doubling the dose of moxifloxacin led to a roughly two times increase in plasma AUC_{0-24}, AUC_{0-6}, and C_{max}. Moxifloxacin concentrations in the cerebrospinal fluid were high and above the limit of quantification in all patients from whom samples of cerebrospinal fluid were

	800 mg (n=16)	400 mg (n=19)	Ratio of 800 mg to 400 mg	p value
Plasma				
AUC_{0-24} (mg.h/L)*	60·4 (45·4–80·3)	28·6 (24·2–33·8)	2·1 (1·6–2·9)	<0·0001†
AUC_{0-6} (mg.h/L)	31·5 (24·1–41·1)	15·1 (12·8–17·7)	2·1 (1·5–2·8)	<0·0001†
C_{max} (mg/L)	7·4 (5·6–9·6)	3·9 (3·2–4·8)	1·9 (1·4–2·6)	<0·0001†
T_{max} (h; median, range)	2 (1–6)	2 (1–6)	..	0·301‡
CSF			..	
C_{max} (mg/L)§	2·43 (1·81–3·27)	1·52 (1·28–1·82)	1·60 (0·34–2·20)	0·006†

Data are number (%) or geometric mean (95% CI), unless otherwise indicated. Moxifloxacin concentrations were measured for plasma AUC_{0-24} and AUC_{0-6} and CSF C_{max} in samples obtained during the first 3 days of treatment. AUC_{0-24}=area under the time-concentration curve up to 24 h after dose. AUC_{0-6}=area under the time-concentration curve up to 6 h after dose. C_{max}=maximum plasma concentration. T_{max}=time to C_{max}. CSF=cerebrospinal fluid. *Could be assessed in 24 patients. †Independent samples t test after log transformation. ‡Wilcoxon rank-sum test. §CSF samples were obtained in 15 patients on moxifloxacin 800 mg and 17 patients on 400 mg. All concentrations were above the limit of quantification of the assay.

Table 3: Pharmacokinetic data for moxifloxacin (n=35)

	All patients (n=60)	Oral rifampicin 450 mg (n=31)			Intravenous rifampicin 600 mg (n=29)		
		No moxifloxacin (n=12)	Moxifloxacin 400 mg (n=10)	Moxifloxacin 800 mg (n=9)	No moxifloxacin (n=10)	Moxifloxacin 400 mg (n=9)	Moxifloxacin 800 mg (n=10)
All adverse events (grade)							
Mild (1 or 2)	22 (37%)	4 (33%)	6 (60%)	2 (22%)	1 (10%)	4 (44%)	5 (50%)
Severe (3 or 4)	12 (20%)	0	1	4 (44%)	3 (30%)	2 (22%)	2 (20%)
Hepatotoxicity (grade)							
Mild (1 or 2)	23 (38%)	4 (33%)	6 (60%)	2 (22%)	1 (10%)	4 (44%)	6 (60%)
Severe (3)	7 (12%)	0	1 (10%)	3 (33%)	1 (10%)	1 (11%)	1 (10%)
Severe (4)	4 (7%)	0	0	1 (11%)	2 (20%)	1 (11%)	0
Haematological changes (grade)							
Mild (1 or 2)	0	0	0	0	0	0	0
Severe (3 or 4)	0	0	0	0	0	0	0
Cardiotoxity (grade)							
Mild (1 or 2)	20 (33%)	2 (17%)	2 (20%)	5 (56%)	3 (30%)	6 (66%)	2 (20%)
Severe (3 or 4)	0	0	0	0	0	0	0
Hypersensitivity (grade)							
Mild (1 or 2)	2 (3%)	0	0	0	1 (10%)	0	1 (10%)
Severe (3 or 4)	1 (2%)	0	0	0	0	0	1 (10%)

Data are number (%).

Table 4: Adverse events

obtained. 800 mg moxifloxacin resulted in 1·6 times higher concentrations in the cerebrospinal fluid (table 3).

Within the first 2 weeks of the study, 57% of patients had adverse events that were possibly or probably related to study drug (table 4). Hepatotoxicity of all grades seemed to be equally distributed between rifampicin standard-dose and high-dose groups, and between the moxifloxacin standard-dose and high-dose groups. Grade 3 transaminase increases (n=7) were transient in all patients, despite continued antituberculous treatment. In accordance with our protocol, treatment was interrupted in patients with grade 4 hepatotoxicity. Haematological toxicity (thrombocytopenia, anaemia, or leucopenia) did not occur. Mild QTc prolongation occurred in 20 patients (33%), including 15 (39%) of 38 patients given moxifloxacin (table 4). Three patients, all in the rifampicin high-dose group, had a hypersensitive reaction. Two reactions were mild and resolved within 3 days without stopping the drugs. One patient developed an anaphylactic shock on the first day of drug administration while receiving high-dose rifampicin and high-dose moxifloxacin, and died within 2 h after drug administration.
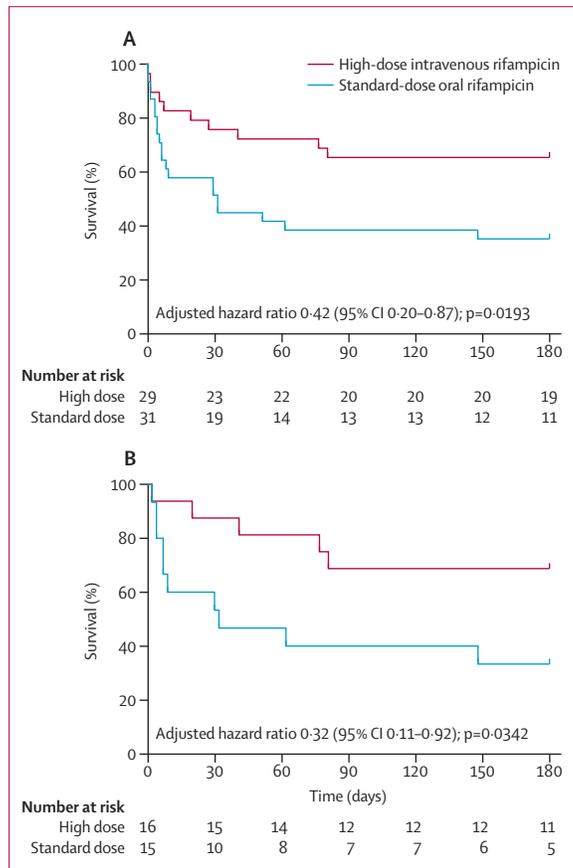
None of the patients were lost to follow-up. 30 patients (50%) died within 6 months, mostly in the first few weeks of treatment. For those who died within the 1 month follow-up (n=22), the main cause of death was respiratory failure (n=9), and then neurological deterioration (n=7), sepsis (n=2), and anaphylaxis (n=1). Cause of death was uncertain in the remaining three patients. Mortality was much lower in patients in the rifampicin high-dose group (figure 2A), and when only patients with culture-confirmed tuberculous meningitis were analysed (figure 2B). Table 5 shows the mortality for the various drug regimens. The effect of rifampicin was similar in both moxifloxacin groups and there was no interaction between the two drugs, confirmed with Cox regression analysis (p=0·54). However, the statistical power in this study was too small to exclude possible interaction between the two interventions. The cumulative 6 month mortality was 65% in patients in the rifampicin standard-dose group versus 34% in the high-dose group. In the multivariable analysis, corrected for moxifloxacin use, HIV status, and GCS at baseline, high-dose rifampicin remained a significant and strong predictor of survival (table 6). In patients with culture-confirmed tuberculous meningitis, drug resistance did not affect outcome; resistance to streptomycin was present in two patients, but no resistance to rifampicin or isoniazid was noted (data not shown). Patients in the high-dose rifampicin group had more rapid resolution of coma (median 4 days [IQR 2–8] vs 5 days [3–7]). Also, more patients in this group had a complete neurological recovery after 6 months of treatment (nine [31%] of 29 vs four [13%] of 31).

Figure 2: Survival according to rifampicin treatment in all 60 patients (A) and in 31 bacteriologically proven cases of tuberculous meningitis (B)

	Oral rifampicin 450 mg	Intravenous rifampicin 600 mg	Total
Ethambutol 750 mg	7/12 (58%)	3/10 (30%)	10/22 (45%)
Moxifloxacin 400 mg	6/10 (60%)	2/9 (22%)	8/19 (42%)
Moxifloxacin 800 mg	7/9 (78%)	5/10 (50%)	12/19 (63%)
Total	20/31 (65%)	10/29 (34%)	30/60 (50%)

Data are n/N (%). All patients received standard dose isoniazid, pyrazinamide, and adjunctive corticosteroids.

Table 5: 6 month mortality by rifampicin regimen

	Deaths	Univariable	Multivariable	p value
Oral rifampicin 450 mg (n=31)	20 (65%)	1·00	1·00	0·03*
Intravenous rifampicin 600 mg (n=29)	10 (34%)	0·42 (0·20–0·91)†	0·42 (0·20–0·91)†	..
No moxifloxacin (n=22)	10 (45%)	1·00	1·00	0·55‡
Moxifloxacin 400 mg (n=19)	8 (42%)	0·74 (0·29–1·89)§	0·76 (0·30–1·94)§	..
Moxifloxacin 800 mg (n=19)	12 (63%)	1·40 (0·60–3·25)§	1·27 (0·53–3·02)§	..
HIV positive (n=7)	4 (57%)	..	1·80 (0·59–5·53)	0·31
Glasgow Coma Scale at baseline	..	..	0·82 (0·68–0·99)	0·04

Data are number (%) or hazard ratio (95% CI), unless otherwise indicated. *For differences between both rifampicin doses. †Patients given 400 mg, 800 mg, or no moxifloxacin were pooled for comparison of rifampicin doses. ‡For differences between all moxifloxacin doses. §Patients given 450 mg or 600 mg rifampicin were pooled for comparison of different doses of moxifloxacin.

Table 6: 6 month mortality and Cox regression analysis

Discussion

Intensified treatment given for 2 weeks strongly increased drug exposure, did not increase drug-related adverse events, and improved the survival of patients. To our knowledge, this is the first report of a higher dose of intravenous rifampicin in patients with tuberculous meningitis (panel). Previous research has shown that rifampicin, a key drug for treatment of tuberculous meningitis, does not penetrate well into the cerebrospinal fluid.[7] Rifampicin concentrations in cerebrospinal fluid have been reported in 18 studies and only in seven of these studies were mean or individual rifampicin concentrations of more than 1·0 mg/L in cerebrospinal fluid recorded at any timepoint.[7] Indeed, patients given standard-dose oral rifampicin in our trial had moderately low concentrations in plasma and very low concentrations in the cerebrospinal fluid. Of note, rifampicin concentrations in plasma and cerebrospinal fluid cannot be compared directly because plasma concentrations refer to total (ie, protein-bound plus unbound) rifampicin, whereas only the unbound (active) fraction penetrates the cerebrospinal fluid because this fluid has a very low protein content compared with plasma. A 1·3 times higher dose of rifampicin given intravenously led to roughly three times higher plasma AUC_{0-6} and C_{max} values

and also three times higher drug concentrations in the cerebrospinal fluid. In a previous study, we noted a non-linear (1·65 times) average increase in systemic exposure to rifampicin when the daily oral dose was increased 1·3 times from 450 mg to 600 mg.[8] In another study, we assessed that rifampicin 450 mg intravenously resulted in a 40% higher drug exposure than the same dose given orally.[27] Therefore, the higher exposure to rifampicin in our study suggests a combination of a higher dose, intravenous administration, and non-linear pharmacokinetics of this antibiotic. This increase in rifampicin exposure might be relevant because the antibiotic has exposure-dependent effects.[5,6] Average rifampicin concentrations were lower than in patients with pulmonary tuberculosis taking a similar oral dose of rifampicin in the same setting,[8] possibly because of lower absorption when rifampicin is given through a nasogastric tube or when patients are severely ill.

Another possible approach for improving outcome of tuberculous meningitis might be the use of more effective antituberculous drugs like fluoroquinolones. After a pharmacokinetic study in 61 patients,[26] a phase 3 trial is now underway to assess whether a combination of levofloxacin with oral rifampicin 15 mg/kg improves survival of patients with tuberculous meningitis.[10] We assessed another fluoroquinolone, moxifloxacin, which might have better pharmacokinetic properties,[17] and stronger activity against *M tuberculosis* than did three other fluoroquinolones (ofloxacin, sparfloxacin, and ciprofloxacin) in animals.[12] Our study is the first in which the pharmacokinetics of moxifloxacin in the plasma and cerebrospinal fluid were assessed in a large series of patients with tuberculous meningitis. A higher dose of moxifloxacin (800 mg), which might be more potent, led to an almost proportional increase in drug concentrations in the plasma and cerebrospinal fluid.

Increasing the dose of rifampicin and moxifloxacin did not seem to greatly increase toxicity, which is in agreement with data for the use of a higher dose of rifampicin for tuberculosis[9] and other indications and with the few data available for high-dose moxifloxacin.[17,28]

Although our study was not powered to detect a difference in mortality, high-dose intravenous rifampicin, when given for the first 2 weeks, led to a roughly 50% reduction in 6 month mortality. Moxifloxacin did not seem to be associated with a survival benefit. It should be noted that mortality in patients given standard-dose rifampicin was higher than in some other studies—eg, 36·5% in the landmark corticosteroid trial from Vietnam.[22] One contributing factor to the fairly high mortality in our study might be that our study population consisted of mostly patients with very advanced disease. Only 7% of our patients presented with BMRC grade 1 tuberculous meningitis (table 1), compared with 32·2% in the Vietnam study. In patients given corticosteroids in the Vietnam study,[22] the mortality was 16·7% in patients with grade 1 tuberculous meningitis, 31·1% with grade 2, and 54·8%

Panel: Research in context

Systematic review

We searched PubMed for articles published up to Sept 12, 2012, with the search terms "tuberculous meningitis", "TB meningitis", OR "high-dose rifampicin", in combination with ("randomized controlled trial"[Publication Type] OR ("randomized"[Title/Abstract] AND "controlled"[Title/Abstract] AND "trial"[Title/Abstract])), and "tuberculous meningitis" OR "TB meningitis" with "moxifloxacin". 69 studies were identified. No published data for patients with tuberculous meningitis given high-dose rifampicin were found, although the trial protocol of an ongoing assessment of high-dose oral rifampicin with levofloxacin was described in one study.[10] The pharmacokinetics of regimens containing four different fluoroquinolones were compared in 61 patients with tuberculous meningitis in a randomised study.[26] We identified a systematic review of high-dose rifampicin in patients with pulmonary tuberculosis.[9] Of 14 trials (4256 participants) included in this systematic review, 12 were done before 1980, and the only recent study judged to be of high quality was done by our group.[8] The pharmacokinetics of moxifloxacin in plasma and cerebrospinal fluid were described in four patients.[17]

Interpretation

Our study is the first in which intensified antibiotic treatment including high-dose rifampicin was assessed in patients with tuberculous meningitis. The findings show that an increased dose of rifampicin, administered intravenously for the first 2 weeks, might improve the outcome of patients with tuberculous meningitis.

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with grade 3. In our study, the respective values for mortality were 25% (one of four), 50% (24 of 49), and 71% (five of seven).

Our study has several limitations. Because of the high early mortality, pharmacokinetic data were not available for all patients. Also no serial lumbar punctures were done, so no pharmacokinetic curves could be generated for cerebrospinal fluid. The apparent mortality benefit of high-dose intravenous rifampicin, although significant, should be interpreted with caution because of the size of the study. Since this study was open label we cannot exclude potential bias in people providing treatment and care for the patients. Despite these limitations, we feel that our results challenge the current treatment model for tuberculous meningitis. Definition of the optimum regimen, which might be given for more than 2 weeks and include an even higher dose of oral (rather than intravenous) rifampicin, would help implementation of intensified treatment for tuberculous meningitis in settings where it is most needed.

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