SciMedCentral

Clinical Research in Infectious Diseases

Research Article

The Comparison of Conventional and Novel Fixed Dose Combination oof Rifampicin and Isoniazid to Improve Bioavailability of Rifampicin for Treatment of Tuberculosis: A Randomized Controlled Trial

Sanjeev Sinha[1]*, Raghunandan P[1], Rashmita Pradhan[1], Shishoo CJ[2], Manish Nivsarkar[2], Path H[2], Samantaray JC[3], Kamal Kishore[4] and Pandey RM[5]

[1]*Department of Medicine, All India Institute of Medical Sciences, India*
[2]*National Institute of Pharmaceutical Education and Research (NIPER), Ahmedabad and B.V.Patel Pharmaceutical Education and Research Development (PERD) Centre, India*
[3]*Department of Microbiology, All India Institute of Medical Sciences, India*
[4]*Department of Pharmacology, All India Institute of Medical Sciences, India*
[5]*Department of Biostatistics, All India Institute of Medical Sciences, India*

Corresponding author
Sanjeev Sinha, MD Additional Professor Department of Medicine, All India Institute of Medical Sciences Ansari Nagar, New Delhi 110029, India, Tel: 91-11-26594440; Fax: 91-11-26588866; Email: drsanjeevsinha2002@yahoo.com

Submitted: 17 March 2014

Accepted: 02 May 2014

Published: 15 May 2014

Keywords
- Anti-tubercular therapy
- Fixed-dose combination
- Tuberculosis
- Rifampicin

Abstract

Background: Fixed-Dose Combinations (FDCs) of anti-tubercular drugs have been recommended as a step towards ensuring better treatment and compliance of patients receiving Anti-Tubercular Therapy (ATT). However, a major concern with FDCs has been low bioavailability of rifampicin due to interaction with isoniazid in the stomach. A novel FDC of gastro-retentive rifampicin and delayed release isoniazid was developed to overcome this interaction.

Methods: The study was a parallel-group, open-label, randomized controlled trial conducted at a tertiary referral centre in northern India. Patients were randomized to receive daily treatment with the conventional FDC dosage formulation or the novel FDC formulation of rifampicin and isoniazid as a part of 4 drug ATT regimen. The outcome measures were sputum conversion rates, radiological response and clinical response. Drug levels of rifampicin and isoniazid were also measured and compared at various time points.

Results: Of the 105 patients who were randomized 55 received the conventional FDC formulation while 50 received the novel FDC formulation. Of the 105 participants, 51 (48.6%) had PTB with the rest having extra-pulmonary tuberculosis (EPTB). 26 of the 51 (51.0%) PTB patients tested positive for tuberculosis either in culture or in sputum microscopy. Two patients in group A and one patient in group B had persistent sputum positivity at the end of 6 months of treatment. None of them were sputum positive at the end of 12 months. Of the 87 patients could be assessed at the end of 6 months treatment, 10/42 (23.8%) of the patients in group A and 13/45 (28.9%) of the patients in group B had some evidence of disease activity at the end of 6 months of treatment on the CT scan or in the Chest X-Ray. A total of 6 (5.8%) patients, three in each group (5.6% in group A and 6.4% in Group B) experienced treatment failure. Of these 3 were classified as treatment failure due to radiological deterioration and 3 due to persistent culture positivity. There was no significant difference in the microbiological, clinical or radiological response rates between the two groups. There was no significant difference in the plasma concentrations of rifampicin and isoniazid at various time points between the two groups.

1.4. Conclusion: In conclusion, we found no difference in the clinical efficacy of rifampicin and isoniazid drug levels of the novel FDC formulation as compared to the conventional FDC formulation. Further studies are required with larger sample size to study the usefulness of novel FDC formulation.

Cite this article: *Sinha S, Raghunandan P, Pradhan R, Shishoo CJ, Nivsarkar M, et al. (2014) The Comparison of Conventional and Novel Fixed Dose Combination oof Rifampicin and Isoniazid to Improve Bioavailability of Rifampicin for Treatment of Tuberculosis: A Randomized Controlled Trial. Clin Res Infect Dis 1(2): 1009.*

INTRODUCTION

Tuberculosis constitutes a major public health problem with an estimated 8.7 million new cases and 1.4 million deaths every year. Worldwide, 3.7% of new cases and 20% of previously treated cases were estimated to have Multi Drug Resistance Tuberculosis (MDR-TB) [1]. This emergence of drug resistant tuberculosis presents a major threat to the future success of TB control. Drug resistance in most tuberculosis patients predominantly arises as a result of poor compliance with medications and multiple interruptions of treatment. As a solution to this problem World Health Organization (WHO) and International Union Against Tuberculosis Lung Disease (IUATLD), together with their partners, recommend the use of Fixed-Dose Combination (FDC) formulations of the essential anti-tuberculosis drugs as one further step to ensure adequate treatment of patients. FDCs improve patient compliance, prevent monotherapy and thereby decrease risk of emergence of MDR-TB, simplify treatment regimens, simplify drug supply chain management and prevent misuse of rifampicin [2].

The use of FDC tablets is widespread in India, accounting for 62% of the rifampicin used in the private health sector [3]. However, the quality of FDCs with respect to variable bioavailability is a major issue. Poor bioavailability of rifampicin from a number of dosage forms of rifampicin and its combination with isoniazid continues to be a subject of much concern. The results of a series of studies have shown that while some FDC formulations had acceptable rifampicin bioavailability, others did not [4]. One of the reasons for the poor bioavailability of the fixed dose combination is enhanced degradation of rifampicin in acidic medium leading to the formation of 3-formyl rifamycin SV (3-FRSV) which reacts with isoniazid to form isonicotinyl hydrazone of rifampicin [5,6]. Furthermore, studies have shown that rifampicin is well absorbed in the stomach while isoniazid is well absorbed in all segments of the small intestine [7].

The National Institute of Pharmaceutical Education and Research (NIPER, Ahmedabad, India), developed a novel FDC form of rifampicin and isoniazid to minimize this interaction between rifampicin and isoniazid in stomach, wherein rifampicin has been formulated for release in the stomach and isoniazid has been formulated for exclusive release in intestine with minimal contact of these two drugs in the solid dosage. Rifampicin also have an extended release via a floating mechanism; to increase the duration of action. This novel FDC form is a gelatine capsule which comprises of pellets of immediate release form of rifampicin, a tablet of gastro-retentive modified release rifampicin and delayed release pellets of isoniazid.

Several studies have been conducted to assess the bioavailability, acceptability, or microbiological efficacy of rifampicin and isoniazid with or without pyrazinamide administered in a FDC for daily or intermittent use [8-12]. Moreover, several clinical trials have also demonstrated the benefits of FDCs [13-15]. The objective of this open labelled randomized control study was to assess the bioequivalence of the two FDC dosage forms and compare their clinical efficacy.

MATERIAL AND METHODS

Study design

The study was a parallel-group, open-label, randomized controlled trial conducted between September 2010 and May 2013 at a tertiary referral centre in northern India. This was a pilot study. The trial did not have a planned sample size and was a sample of convenience. Given the number of patients who completed the study follow-up at the end of the trial, the power of the study was less than 50%. The study had two components, the clinical efficacy of the two FDC dosage forms and the study of bioequivalence of the two FDC dosage forms. The study was approved by the institutional ethics committee of the All India Institute of Medical Sciences. Before study enrolment, the conditions of the study were explained to the patients according to information contained in a patient information sheet and an informed consent was obtained.

Patient Selection and randomization

Patients with newly diagnosed Pulmonary (PTB) or Extra-Pulmonary Tuberculosis (EPTB) were admitted to the study if they were 18 years or older, had received either no previous antituberculosis chemotherapy, had a firm home address readily accessible for visiting and intended to remain there during the entire study period, and had provided written informed consent to participate in the study. Patients were not eligible if they were considered unlikely to survive the initial weeks of treatment; were HIV positive; severe cardio-pulmonary disease, hepatic or renal disease; blood disorders, or peripheral neuritis; were known to be pregnant or were breast feeding; had a history of alcoholism; or had any contraindication to any medications used in the study. Patients were randomly assigned to receive either a control (Group A) or test (Group B) regimen using a computer generated random number table.

Dosing and regimen

The patients randomized to the test regimen (Group B) were administered rifampicin and isoniazid in the form of the novel FDC dosage capsule while the control regimen (Group A) consisted of the same drugs administered in the form of conventional FDC capsules. The doses were given according to recommendations from the World Health Organization (WHO) and RNTCP guidelines, based on the weight of the patient in kilograms at the time of starting treatment without adjustment for weight change during treatment [16,17]. The dosing regimens consisted of an initial intensive phase of 8 weeks of daily rifampicin, isoniazid, pyrazinamide, and ethambutol followed by 18 weeks of daily rifampicin and isoniazid. The intensive phase was extended by four weeks if the patient was tested sputum positive for M. *tuberculosis* at 2 months or detected to have worsening radiological response. The continuation phase was extended if the patient had inadequate clinical, radiological or microbiological response to the treatment regimen.

Initial visit

Two sputum specimens were collected before the start of treatment for examination by microscopy and culture. A chest radiograph or CT scan (if required) was obtained and kept for independent assessment in the case of pulmonary tuberculosis. CT scans of the affected regions were obtained in patients with EPTB. Participants with EPTB also received histological or microbiological confirmation using fine-needle aspiration biopsy or fluid aspiration. Patients were required to provide a

blood sample to test for human immunodeficiency virus (HIV) infection after pre-test counselling; the result was communicated to patients if they wished to receive it, and post-test counselling was provided. Those who were HIV-infected were excluded from the trial and referred to the appropriate local HIV care services. Information was collected on antiretroviral treatment in addition to treatment for tuberculosis. Initial tests also included blood chemistries, renal and liver function tests and a haemogram. Venous blood samples were collected before administration and 1 and 24 h after administration of the FDC drug. The samples were centrifuged and the plasma stored in vials containing ascorbic acid at −80°C to prevent oxidation of rifampicin until analyzed.

Follow-up

Patients were seen every week till the end of treatment and then every two months for a total of 12 months of follow-up. At each visit during treatment the patients were provided with a one week supply of drugs and their adherence to treatment was reviewed. Patients who missed an appointment were contacted through a telephone call by nurse and trial assistant and asked to return to the study clinic. Blood chemistries, renal and liver function tests and a haemogram were obtained at the end of 2 weeks, 2, 4, 6, 9 and 12 months of follow-up. Appropriate imaging was obtained at the end of the intensive phase and at the completion of treatment. Sputum was obtained for microscopy and culture at the end of 2 months and at the end of 6 months of treatment as per WHO and RNTCP guidelines [16,17]. Venous blood samples were collected 8h after the administration of the FDC drug at the end of 2,3, 4 and 6 months of treatment. The samples were centrifuged and the plasma stored in vials containing ascorbic at −80°C until analyzed.

Bioequivalence study measurements

The concentration of rifampicin, isoniazid, ethambutol and pyrazinamide in human plasma were estimated using a precise and accurate high performance Liquid Chromatography (LC-MS) procedure. The procedure was validated according to in house method validation Standard of Procedure (SOP). The analysis was performed using LC-MS system using rifabutin and 6-aminonicotinic acid as Internal Standard (IS). The assays of all above four drugs were done. The drug was extracted from plasma using organic solvent and injected in to LC-MS system to determine the concentration of unknown sample. Extraction was done by adding 100 µl of plasma to 50µl of the Internal Standard (IS) and vortexing the mixture. This was then extracted with 250µl of acetonitrile. The organic fraction was separated and 10µl of this sample was injected into LC-MS system.

The Analyst software was used for evaluation of the chromatograms. The calibration curve standards and quality control standards were prepared with chromatographically screened plasma blanks, which were found to be free from significant interferences at the retention times of drug and IS. The Calibration Curves (CC) and Quality Controls (QC) were prepared and the samples were analyzed and evaluated according to the procedure described in the Standard Operation Procedure (SOP). The Calibration Curve (CC) standards and Quality Control (QC) standards in-study validation met the acceptance criteria, demonstrating satisfactory performance of the method during the analysis of study subject samples.

Statistical analysis

Data were recorded on a pre-designed data sheet and managed on an 'Excel' spread sheet. All entries were doubly checked for any possible recording error. Mean, frequency and medians were calculated for all quantitative variables along with the respective standard deviations and Interquartile ranges. The comparisons between drug levels in the two groups were made using Wilcoxon-ranksum test given the non-normal distribution of the data. The generalised estimation equations were used to find out the change in weight and biochemical parameters. The radiological and microbiological outcome variables which were categorical variables were analyzed using χ^2 test or Fischer's exact test. Statistical analysis was performed using statistical software package STATA version 11.0 [(intercooled version), Stata Corporation, Houston, Texas, USA].

RESULTS

Baseline characteristics

A total of 168 patients were screened. Of these, 63 were excluded from the study. There remained 105 patients who were randomized (55 in the group A, 50 in group B (Figure 1). Baseline characteristics (Table 1) were similar in the 2 groups except for sex where a significantly higher proportion of men were found to be in the patients receiving the novel FDC dosage form (group B). Of the 105 participants, 51 (48.6%) had PTB with the rest having EPTB. 26 of the 51 (51.0%) PTB patients tested positive for tuberculosis either in culture or in sputum microscopy.

Microbiological outcomes

Of the 26 patients who were found to be sputum positive

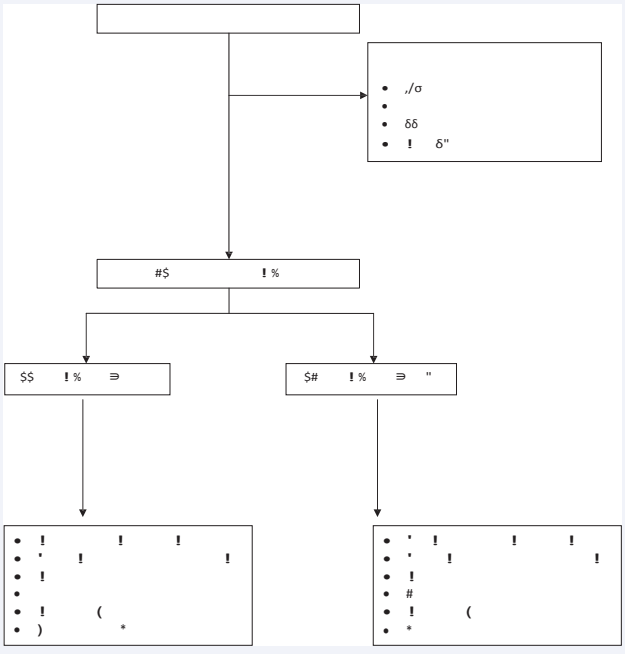

Figure 1 Randomization and Study Flow.

either by culture or sputum examination at any time during their follow-up, 9 patients (4 and 5 in Group A and Group B respectively) were found to be sputum/culture positive at the end of 2 months of treatment. Two patients in group A and one patient in group B had persistent sputum positivity at the end of 6 months of treatment (Table 2). Further culture sensitivity data revealed these patients to have MDR-TB. None of the patients were sputum positive at the end of 12 months, however this does not include the 3 MDR-TB patients. There was no significant difference in sputum conversion rates between the two groups.

Radiological outcomes

Out of the 105 participants, the radiological response of 87 patients could be assessed at the end of 6 months treatment. 10/42 (23.8%) of the patients in group A and 13/45 (28.9%) of the patients in Group B had some evidence of disease activity at the end of 6 months of treatment on the CT scan or in the Chest X- Ray. Only one of the patients had definite evidence of disease activity at the end of one year of treatment. There was no significant difference in the two treatment groups in terms of

Table 1: Baseline characteristics of the two patient groups.

Variable	Group A N=55	Group B N=50	P value
Age, years: Mean ± SD	36 ± 16.5	34 ± 15.6	0.48
Gender, number (%):			
Male Female	28 (50.9) 27 (49.1)	14 (28.0) 36 (72.0)	0.02
Weight, kg: Mean ± SD	53 ± 13	54 ± 12	1.00
Hemoglobin, g/dL Mean ± SD	11.3 ± 1.7	12.0 ± 2.0	0.09
AST, IU/L: Median (Range)	22 (10 - 76)	31 (02 - 108)	0.13
ALT, IU/L: Median (Range)	28 (17 - 98)	31 (16 - 74)	0.27
Type of Tuberculosis, number (%):			
PTB	27 (49.1)	24 (48.0)	
EPTB-LN	13 (23.6)	09 (18.0)	
Disseminated TB	05 (9.1)	07 (14.0)	
EPTB-Pleura	08 (14.6)	09 (18.0)	0.54
EPTB-GU	02 (3.6)	0 (0.0)	
EPTB-Abdominal	0 (0.0)	1 (2.0)	
Sputum microscopy for AFB, number (%):			
Negative	20 (36.4)	25 (50.0)	
Positive	11 (20.0)	12 (24.0)	0.16
Not applicable	24 (43.6)	13 (26.0)	
Plain Chest Radiograph, number (%):			
No active disease Active Disease	09 (16.4) 41 (74.6)	09 (18.4) 39 (78.0)	0.61
Not assessable	05 (9.1)	02 (4.1)	
CT Scan, number (%):(n=62)			
No active disease Active Disease	0 (0.0) 34 (97.1)	0 (0.0) 27 (100.0)	1.00
Not assessable	01 (2.9)	0 (0.0)	
Histopathologial Examination, number			
(%):(n=37) AFB Positive Necrotizing Granuloma Non-necrotizing granuloma Reactive lymph Node Non-Diagnostic	6 (27.3) 4 (18.2) 3 (13.6) 1 (4.6) 8 (36.4)	4 (26.7) 4 (26.7) 2 (13.3) 0 (0.0) 5 (33.3)	0.99

Abbrivations: SD: Standard Deviation; AST: Aspartate Amniotransferase; ALT: Alanine aminotransferase ; PTB: Pulmonary Tuberculosis ; EPTB: Extra-pulmonary tuberculosis; LN: Lymph Nodal ; GU: Genitourinary

Table 2: Primary Outcomes as assessed at different time points.

Variable	Time	Result	Group A N (%)	Group B N (%)	P-value
Sputum microscopy	Baseline N=105	Negative	20 (36.4)	25 (50.0)	0.16
		Positive	11 (20.0)	12 (24.0)	
		Not applicable	24 (43.6)	13 (26.0)	
	2 months N=99	Negative	18 (36.0)	21 (42.9)	0.46
		Positive	02 (4.0)	04 (8.2)	
		Not applicable	30 (60.0)	24 (48.9)	
	6 months N=97	Negative	15 (30.6)	20 (41.7)	0.50
		Positive	02 (4.1)	01 (2.1)	
		Not applicable	32 (65.3)	27 (56.2)	
Sputum Culture	Baseline N=105	Negative	21 (38.2)	27 (54.0)	0.05
		Positive	07 (12.7)	10 (20.0)	
		Not applicable	27 (49.1)	13 (26.0)	
	2 months N=99	Negative	15 (30.0)	20 (40.8)	0.41
		Positive	04 (8.0)	05 (10.2)	
		Not applicable	31 (62.0)	24 (49.0)	
	6 months N=97	Negative	13 (26.5)	20 (41.7)	0.34
		Positive	02 (4.1)	01 (2.1)	
		Not applicable	34 (69.4)	27 (56.3)	
Chest Plain Radiograph	Baseline N=105	No active disease	09 (16.4)	09 (18.0)	0.61
		Active disease	41 (74.6)	39 (78.0)	
		Not assessable	05 (9.1)	02 (4.0)	
	2 months N=98	No active disease	25 (50.0)	21 (43.8)	0.50
		Active disease	18 (36.0)	23 (47.9)	
		Not assessable	7 (14.0)	04 (8.3)	
	6 months N=96	No active disease	41 (83.7)	35 (74.5)	0.46
		Active disease	04 (8.2)	08 (17.0)	
		Not assessable	04 (8.2)	04 (8.5)	
CT Scan	Baseline N=62	No active disease	0 (0.0)	0 (0.0)	1.00
		Active disease	34 (97.1)	27 (100.0)	
		Not assessable	1 (2.9)	0 (0.0)	
	6 months N=61	No active disease	21 (63.6)	14 (50.0)	0.46
		Active disease	8 (24.3)	11 (39.3)	
		Not assessable	04 (12.1)	03 (10.7)	
Composite Radiological Outcome	6 months N=97	Inadequate response	10 (20.4)	14 (29.2)	0.24
		Adequate response	32 (65.3)	32 (66.7)	
		Not assessable	07 (14.3)	02 (4.3)	

radiological response. Individual responses to CXR and CT have been shown in Table 2.

Plasma drug concentrations

The rifampicin concentrations were measured at 0,1 and 24 hours after the FDC administration on day 1, and 8 hours after administration at the end of 2 months, 3 months, 4 months and 6 months of treatment. There was no significant difference in the concentrations of rifampicin or isoniazid at any of these time points between the two groups (Figure 2A, 2B).

Other outcomes

Two of the patients expired while on treatment. Both of the deaths were attributed to tuberculosis and both occurred within the first month of treatment. Both patients were on the conventional FDC dosage form (Group A). A total of 6 (5.8%) patients, three in each group (5.6% in group A and 6.4% in Group B) experienced treatment failure. Of these 3 were classified as treatment failure due to radiological deterioration and 3 due to persistent culture positivity. The median duration of treatment in the two groups was 188 days (range – 178-417 days) in

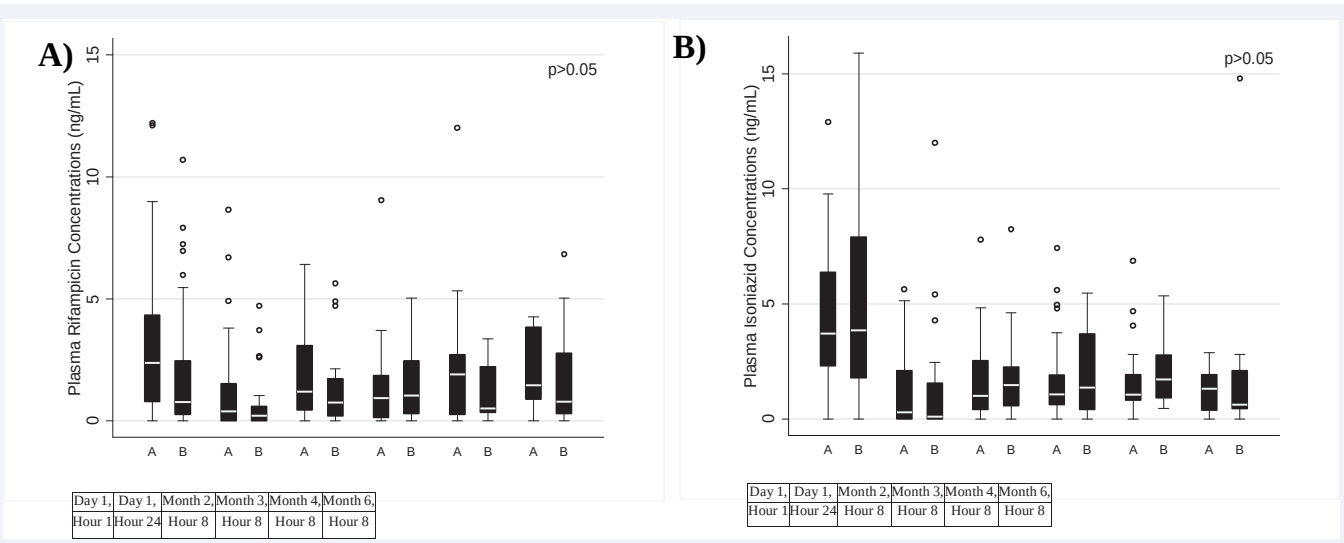

Figure 2 **A:** Plasma rifampicin concentrations at various time points in the two groups*; A- Group A (Conventional FDC); B-Group B (Novel FDC). **B:** Plasma isoniazid concentrations at various time points in the two groups*; A- Group A (Conventional FDC); B-Group B (Novel FDC).

Table 3: Laboratory and clinical parameters during follow-up.

Variable	Time	Group A (n=55)	Group B (n=50)	P-value
Weight (Kg)	Baseline	53 ± 13.5	53 ± 12.4	1.00
	2 months	55 ± 11.1	55 ± 12.0	0.81
	4 months	56 ± 11.8	57 ± 12.6	0.70
	6 months	57 ± 12.1	57 ± 12.1	0.70
	12 months	59 ± 11.2	60 ± 10.0	0.66
Hemoglobin (g/dL)	Baseline	11.3 ± 1.7	12.0 ± 2.0	0.09
	2 weeks	11.8 ± 1.8	12.4 ± 2.0	0.17
	2 months	12.4 ± 1.8	12.9 ± 1.8	0.28
	4 months	12.8 ± 1.9	13.2 ± 2.0	0.39
	6 months	12.7 ± 2.1	13.5 ± 1.9	0.14
	12 months	13.4 ± 1.6	13.8 ± 1.8	0.41
AST (IU/L)*	Baseline	22 (10 - 76)	31 (2 - 108)	0.13
	2 weeks	31 (10 - 537)	43 (11 - 558)	0.10
	2 months	31 (10 - 184)	31 (10 - 172)	0.85
	4 months	30 (10 - 142)	29 (8 - 147)	0.60
	6 months	33 (10 - 332)	33 (8 - 92)	0.83
	12 months	26 (11 - 108)	27 (5 - 113)	0.74
ALT (IU/L)*	Baseline	28 (17 - 98)	31 (16 - 74)	0.27
	2 weeks	38 (10 - 272)	38 (18 - 442)	0.32
	2 months	34 (9 - 140)	33 (18 - 185)	0.79
	4 months	32 (15 - 136)	29 (9 - 152)	0.55
	6 months	37 (17 - 235)	30 (12 - 146)	0.12
	12 months	29 (10 - 88)	27 (18 - 70)	0.41
ESR (mm/hr)*	Baseline	38 (9 - 134)	35 (2 - 139)	0.22
	2 weeks	30 (2 - 114)	31 (2 - 138)	0.29
	2 months	28 (2 - 117)	25 (2 - 60)	0.28
	4 months	22 (2 - 55)	20 (2 - 44)	0.48
	6 months	20 (2 - 78)	20 (2 - 38)	0.17
	12 months	16 (2-40)	12 (4-42)	0.06

* - Variables summary statistics are presented as Median (Range). P values are from Wilcoxon Ranksum test. The rest of the variable summary statistics are mean ± SD. The P values are from GEE analysis.
ESR: Erythrocyte Sedimentation Rate ; AST: Aspartate Amniotransferase; ALT: Alanine aminotransferase

group A and 187 days (range – 177-331 days) in group B with no significant difference observed in the two groups. A total of 34 patients needed extension of treatment beyond 200 days. Of these seventeen (30.9%) were in Group A and seventeen (34.0%) were in Group B with no significant difference between the two groups. Mostly these patients have EPTB and disseminated tuberculosis. A weight gain of 4.2kg (95% CI: 3.5-5.0 kg) was observed between baseline and 6 months of treatment. However there was no significant difference between the two groups. The evolution of some of the laboratory parameters have been shown in Table 3. There was also no significant difference in hemoglobin, TLC, platelets, ESR, urea, creatinine, ALT, AST, albumin, bilirubin between the two groups at any time point.

DISCUSSION

In this single-centre open labelled randomized trial and bioequivalence study of a novel FDC dosage form, we found no evidence to indicate that the novel dosage form is inferior to conventional FDC in its clinical efficacy. The clinical data indicated that there is no significant difference in the failure rates or in the clinical, radiological and microbiological response rates between the two dosage forms.

Both WHO and IUALTD encourage the use of FDCs over use of separate drugs and FDCs now a full part of the recently revised WHO treatment guidelines. Two large randomized control trials have demonstrated that FDC regimens are non-inferior to separately administered drugs in terms of efficacy for treatment of tuberculosis [13,18].These large trials had dichotomous end points of favourable (cure) and unfavourable (failure) responses. Both these trials had favourable response rates between 80-85% in both arms at the end of the trial in their intention-to-treat populations. Our trial showed similar response rates in our composite endpoints with cure rates close to the WHO target of 85% at the end of 12 months. Again there was no significant difference in response rates between the two dosage forms.

Of the 26 sputum positive trial participants, 9 of them were sputum culture positive at the end of 2 months of treatment and one patient had been lost to follow-up. Only three of the patients tested sputum culture positive at the end of 6 months of treatment. This corresponds to a sputum conversion rate very similar to those observed in the other FDC trials [13,18,19]. There was no patient who was sputum positive at the end of 12 months of treatment in either group.

The radiological response rates at the end of 6 months as assessed by CT and CXR was around 76.2% and 71.1% in the groups A and B respectively. This is lower than the response rates in the trial reported by Su et al [19]. The radiological response rates were also delayed in a large proportion of patients in our trial. This is most likely due to the large fraction of severe forms of EPTB in our trial. Weight gain is a surrogate marker for clinical response. Weight showed a significant increase in both the arms over the period of 6 months of treatment. However no significant difference was observed between the two groups. Also other clinical parameters showed similar responses between the two groups. Thus there was no difference in the rates of radiological, microbiological or clinical response.

There was no difference in the plasma rifampicin and isoniazid levels at different time points. The rifampicin concentrations in patients receiving the novel FDC was lower at some of the early time points. This difference could be attributed to the fact that the conventional FDC formulations had all the rifampicin as immediate release components while the novel FDC formulation had a significant fraction (350mg) of rifampicin in the form of sustained release pellets. This could explain the lower concentrations of rifampicin (non-significant) in some of the early stages of sampling.

The main strength of our study was that it was a randomized control trial that assessed not only clinical outcomes but also the pharmacokinetics of the ATT regimens at the same time. Another strength of the trial was that we measured both a single composite outcome as well as outcomes in terms of clinical, radiological and microbiological responses. The study also had a few limitations. The sample size is small and in addition, the sample size of the study was based on a target of convenience rather than on power calculations. In conclusion, we found no difference in the clinical efficacy or plasma rifampicin and isoniazid concentrations between the novel FDC formulation and the conventional FDC formulation. Further studies with larger sample size will be needed to ascertain the usefulness of the novel FDC formulation in the clinical practice.

ACKNOWLEDGEMENT

We thank Department of Pharmaceuticals, Ministry of Chemical & Fertilizers, Shastri Bhawan, Government of India, New Delhi, for funding to this study. We also thank and acknowledge the support of research staff during the enrolment of patients.

Authors' contributors

SS provided inputs to the study design, helped in data analysis and interpretation, wrote the manuscript, and did final editing. RP (Raghunandan P) reviewed literature and helped in interpreting data and writing the manuscript. JCS and KK helped in interpreting data, laboratory diagnosis and writing the manuscript. CJS, MN and HP provided inputs to the study design, helped in interpretation of results and measurement of plasma drug concentrations by LCMS. RP (Rashmita Pradhan) helped in the enrolment and follow-up of patients and RMP did data analysis. All authors approved and read the final manuscript.

Trial registration

CTRI/2013/05/003626.

REFERENCES

1. World Health Organization: Global Tuberculosis Report 2012. Geneva: World Health Organization. 2012.
2. Blomberg B, Spinaci S, Fourie B, Laing R. The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. Bull World Health Organ. 2001; 79: 61-68.
3. Catalani E. Review of the Indian market of anti-tuberculosis drugs: focus on the utilisation of rifampicin-based products. Int J Tuberc Lung Dis. 1999; 3: S289-291.
4. Fixed-dose combination tablets for the treatment of tuberculosis: report of an informal meeting held in Geneva. 1999.
5. Shishoo CJ, Shah SA, Rathod IS, Savale SS, Vora MJ. Impaired

bioavailability of rifampicin in presence of isoniazid from fixed dose combination (FDC) formulation. Int J Pharm. 2001; 228: 53-67.

6. Singh S, Mariappan TT, Shankar R, Sarda N, Singh B. A critical review of the probable reasons for the poor variable bioavailability of rifampicin from anti-tubercular fixed-dose combination (FDC) products, and the likely solutions to the problem. Int J Pharm. 2001; 228: 5-17.

7. Mariappan TT, Singh S. Regional gastrointestinal permeability of rifampicin and isoniazid (alone and their combination) in the rat. Int J Tuberc Lung Dis. 2003; 7: 797-803.

8. Gohel MC, Sarvaiya KG. A novel solid dosage form of rifampicin and isoniazid with improved functionality. AAPS PharmSciTech. 2007; 8: E68.

9. Acocella G, Nonis A, Perna G, Patane E, Gialdroni-Grassi G, Grassi C. Comparative bioavailability of isoniazid, rifampin, and pyrazinamide administered in free combination and in a fixed triple formulation designed for daily use in antituberculosis chemotherapy. II. Two-month, daily administration study. Am Rev Respir Dis. 1988, 138: 886–890.

10. Agrawal S, Kaur KJ, Singh I, Bhade SR, Kaul CL, Panchagnula R. Assessment of bioequivalence of rifampicin, isoniazid and pyrazinamide in a four drug fixed dose combination with separate formulations at the same dose levels. Int J Pharm. 2002; 233: 169–178.

11. Ellard GA, Ellard DR, Allen BW, Girling DJ, Nunn AJ, Teo SK, et al. The bioavailability of isoniazid, rifampin, and pyrazinamide in two commercially available combined formulations designed for use in the short-course treatment of tuberculosis. Am Rev Respir Dis. 1986; 133: 1076-1080.

12. Xu J, Jin H, Zhu H, Zheng M, Wang B, Liu C, et al. Oral bioavailability of rifampicin, isoniazid, ethambutol, and pyrazinamide in a 4-drug fixed-dose combination compared with the separate formulations in healthy Chinese male volunteers. Clin Ther. 2013; 35: 161-168.

13. Lienhardt C, Cook SV, Burgos M, Yorke-Edwards V, Rigouts L, Anyo G, et al. Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the Study C randomized controlled trial. JAMA. 2011; 305: 1415-1423.

14. Hong Kong Chest Service/British Medical Research Council. Acceptability, compliance, and adverse reactions when isoniazid, rifampin, and pyrazinamide are given as a combined formulation or separately during three-times-weekly antituberculosis chemotherapy. Am Rev Respir Dis. 1989; 140: 1618-1622.

15. Assessment of a daily combined preparation of isoniazid, rifampin, and pyrazinamide in a controlled trial of three 6-month regimens for smear-positive pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. Am Rev Respir Dis. 1991; 143: 707-712.

16. World Health Organization, Stop TB Initiative (World Health Organization): The Treatment of Tuberculosis Guidelines. Geneva: World Health Organization; 2010.

17. Central TB Division, Indian Medical Association, WHO-India: Training Module for Medical Practitioners. New Delhi: Revised National Tuberculosis Control Programme (RNTCP); 2010.

18. Bartacek A, Schütt D, Panosch B, Borek M, Rimstar 4-FDC Study Group. Comparison of a four-drug fixed-dose combination regimen with a single tablet regimen in smear-positive pulmonary tuberculosis. Int J Tuberc Lung Dis. 2009; 13: 760–766.

19. Su WJ, Perng RP. Fixed-dose combination chemotherapy (Rifater/Rifinah) for active pulmonary tuberculosis in Taiwan: a two-year follow-up. Int J Tuberc Lung Dis. 2002; 6: 1029-1032.

Cite this article

Sinha S, Raghunandan P, Pradhan R, Shishoo CJ, Nivsarkar M, et al. (2014) The Comparison of Conventional and Novel Fixed Dose Combination oof Rifampicin and Isoniazid to Improve Bioavailability of Rifampicin for Treatment of Tuberculosis: A Randomized Controlled Trial. Clin Res Infect Dis 1(2): 1009.