Original Article

Hepatic Safety of High-Dose Rifampicin for Tuberculosis Treatment in TB/HIV Co-infected Patients: A Randomized Clinical Trial

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Abstract

High-dose Rifampicin regimens have been shown to be more effective for tuberculosis (TB) treatment in TB/HIV co-infected patients. This study assessed the hepatic safety of a high-dose Rifampicin regimen among TB/HIV co-infected patients. 811 TB/HIV co-infected patients, antiretroviral treatment (ART) naïve, at least 18 years old with a CD4 T-cell count between 50 and 350 cells/mm^3 were enrolled. Patients with multidrug-resistant tuberculosis were excluded. Patients had received first-line antituberculosis treatment followed by ART after two weeks (arm A) or two months (arm B). In arm C, they received antituberculosis treatment with a high dose of Rifampicin (15 mg/kg/day instead of 10 mg/kg/day) during the TB intensive phase of treatment and ART after two months. The patients performed transaminases (ALT, AST), γ-glutamyl transpeptidase (γ-GT), alkaline phosphatase (ALP), and total bilirubin blood tests. The study outcomes were an elevation of ALT at least 5 times the Upper Limit of Normal (Primary outcome), an isolated elevation grade 4 of AST, γ-GT, ALP, and/or total bilirubin (Secondary outcomes). The patients included were 53.97% men and 2.44% co-infected hepatitis B or C virus. There were no significant differences between ALT, AST, γ-GT, ALP, and total bilirubin between the standard regimens (Arms A and B) and high dose Rifampicin regimen (Arm C). This study showed that a high-dose Rifampicin regimen for TB treatment in TB/HIV co-infected patients was as safe as that of a standard regimen.

Keywords: High dose, Rifampicin, Liver injury, Hepatotoxicity

Introduction

Tuberculosis (TB) is the leading cause of death in HIV-positive patients [1]. In 2018, worldwide, 8.6% of the 10.0 million people with tuberculosis (TB) were living with HIV and 251,000 of them dead from TB/HIV co-infection [1]. The treatment of this co-infection is based on anti-TB multidrug therapy (Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol) combined with antiretroviral therapy (ART).

At a therapeutic dose, first-line anti-TB drugs such as Rifampicin, Isoniazid, and Pyrazinamide are known to be hepatotoxic in patients with comorbidity, liver disease, or those who are concomitantly using other drugs [2, 3]. Hepatotoxicity can also occur in patients carrying one or more genetic variations located inside or near the genes *NAT2*, *CYP2E1*, and *GST*, which encode the enzymes involved in the metabolism of these drugs [4].

Drug-Induced Liver Injuries (DILIs) are rare and sometimes unpredictable conditions. They are manifested by an asymptomatic elevation of transaminases or specific clinical signs and can progress to acute hepatic failure in the absence of proper management. They are a major cause of death and liver transplantation and remain a problem of public health concern requiring international consensus. That is what justifies the design of a set of essential tools by the working group of the Council for International Organizations of Medical Sciences on Drug-Induced Liver Injury (CIOMS DILI) to detect, diagnose, and manage DILIs during the development of the drugs and after their marketing authorization.

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In TB/HIV co-infected patients, the intestinal absorption of first-line anti-TB drugs is reduced, leading to a decrease in their plasma concentrations [5]. In addition, a frequent polymorphism of the *SLCO1B1* (Solute Carrier organic Anion Transporter Family Member 1B1) rs4149032 gene is associated with the reduction in plasma concentrations of Rifampicin [6].

Previous studies have shown that high-dose Rifampicin regimens have better TB treatment outcomes [7-16]. These regimens have been shown to be well tolerated overall [7-16]. However, little is known about their hepatic tolerability in the context of TB/HIV co-infection where ART is associated with TB treatment. Moreover, in conclusion to the systematic review published in April 2021 by Onorato *et al.* [17], the authors suggested that more data was needed to analyze the efficacy and safety of higher doses of Rifampicin in specific subpopulations, such as seropositive subjects and patients with diabetes or mild bodyweight. Thus, studies on high-dose Rifampicin regimens on TB/HIV co-infected patients will contribute to the advancement of the current state of knowledge and improve the management of patients.

The RAFA Trial (PACTR201105000291300) conducted in three West African countries (Benin, Guinea, Senegal) aimed to assess the benefits in terms of mortality reduction of three therapeutic regimens of which one was with high-dose Rifampicin for the treatment of TB. In this study, we assessed the hepatic safety of this regimen in TB/HIV co-infected patients.

Materials and Methods

Study Setting

This study was conducted in three West African countries: Benin, Guinea, and Senegal. Patients were recruited at the National Teaching Hospital for Pulmonary Diseases in Cotonou and Akron Hospital in Porto-Novo (Benin), the Outpatients TB treatment Centre in Dakar (Senegal), and the Pulmonology Department of Ignace Deen Hospital in Conakry (Guinea).

Study Design and Period

This study is a sub-study of the RAFA Trial, a Phase III, open-label, multicentre, randomized, controlled trial with three arms. It was conducted from January 21st, 2011 to January 21st, 2015.

Study participants

The participants were TB/HIV co-infected patients, antiretroviral-naïve, aged at least 18 years with a CD4 T-cell count between 50 and 350 cells/mm^3. All participants signed an informed consent form.

Patients infected with HIV-2, drinking alcohol or under concomitant treatment inconsistent with the study, pregnant or breastfeeding women or those not willing to use a contraceptive method during the study period were not eligible.

Patients diagnosed with multidrug-resistant TB (MDR-TB) during the follow-up were excluded from the study and treated according to the national guidelines of their respective country.

Sample size

1,125 patients were planned to be recruited for the whole RAFA trial. After the recruitment, 811 patients were recruited for this sub-study and 31 were excluded for MDR-TB. Finally, 780 patients remained whose data were analyzed **(Figure 1)**.

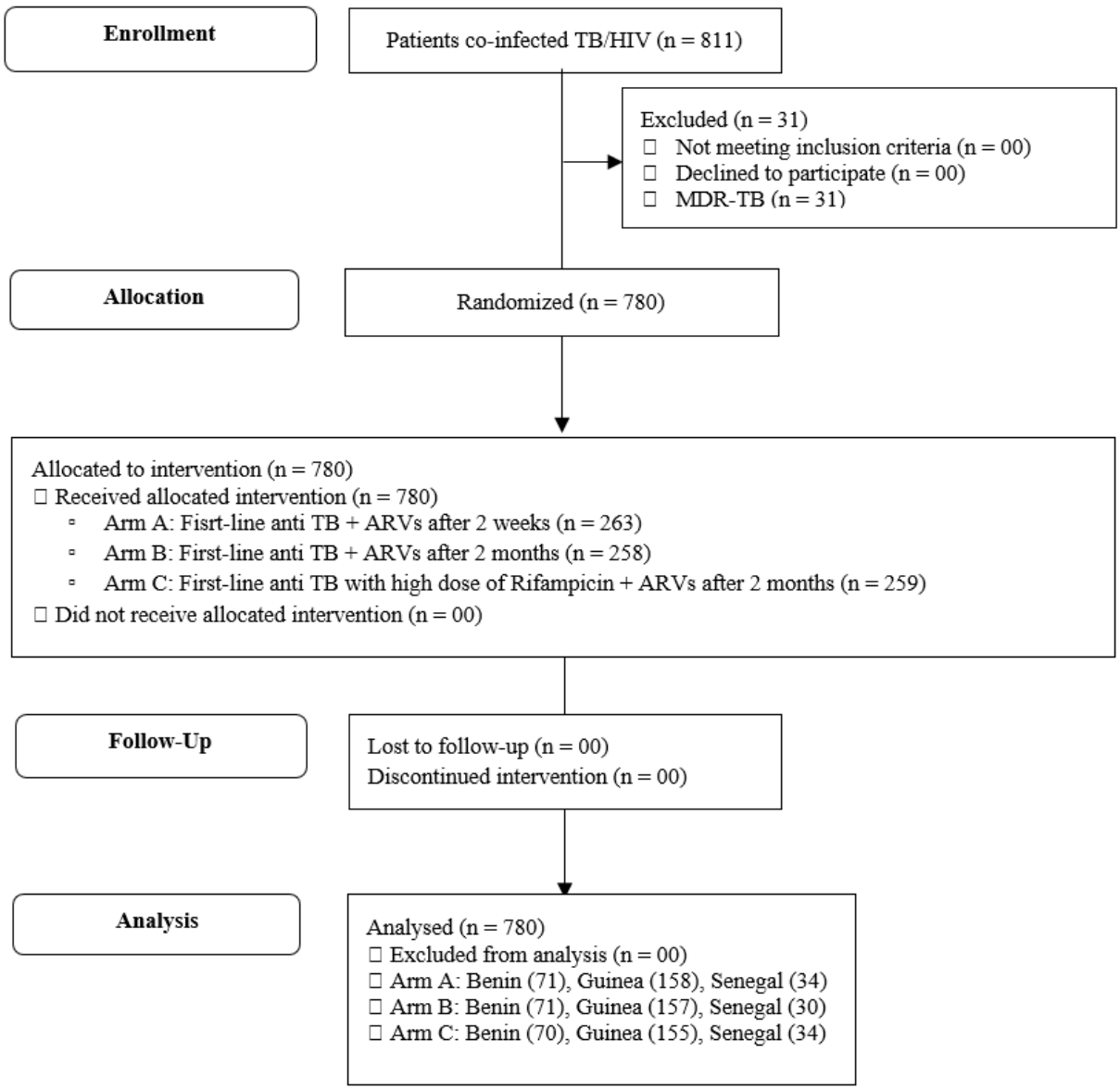

Figure 1. CONSORT Flow Diagram of participants

Drugs given to the study participants were fixed combinations of antituberculosis drugs (RHZE and RH), antiretroviral drugs (2 Nucleoside Reverse Transcriptase Inhibitors (2NRTI) and Efavirenz), and Rifampicin tablets (additional dosage of Rifampicin in the study Arm C) **(Table 1)**. In the RHZE tablets, the drugs' strengths were Rifampicin (150 mg), Isoniazid (75 mg), Pyrazinamide (400 mg), and Ethambutol (275 mg). In the RH tablets, the drug strengths were Rifampicin (150 mg) and Isoniazid (75 mg).

Table 1. Dosages of antituberculosis and antiretrovirals drugs given to the participants

Study arms	Bodyweight		
	< 38 kg	38-54 kg	> 54 kg
	Intensive phase		
Arm A **Arm B**	2RHZE + 2NRTI + EFV	3RHZE + 2NRTI + EFV	4RHZE + 2NRTI + EFV
Arm C	2RHZE + R* + 2NRTI + EFV	3RHZE + R* + 2NRTI + EFV	4RHZE + R* + 2NRTI + EFV
	Continuation phase		
Arm A	2RH + 2NRTI + EFV	3RH + 2NRTI + EFV	4RH + 2NRTI + EFV

Arm B

Arm C

R (Rifampicin, 10 mg/kg/day) ; R*(Additional dose of Rifampicin, 5 mg/kg/day) ; H (Isoniazid, 5 mg/kg/day) ; Z (Pyrazinamide, 25 mg/kg/day) ; E (Ethambutol, 15 mg/kg/day) ; NRTI (Nucleoside Reverse Transcriptase Inhibitors: Tenofovir 300 mg/tablet or Zidovudine 300 mg/tablet and Lamivudine 300 mg/tablet) ; EFV (Efavirenz, 600 mg/day).

Procedures

Randomization lists, stratified by study sites and indicating the randomization number and corresponding treatment arm, were provided prior to the start of the study by a statistician of the London School of Hygiene & Tropical Medicine. The codes were put in sealed envelopes and assigned to patients as they were included in the study.

Each patient received first-line antituberculosis treatment (Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide) followed by initiation of ARVs (Antiretroviral) therapy (2NRTI + EFV) **(Table 1)**.

Patients in arm B had received first-line antituberculosis treatment followed by ARVs two months after initiation of antituberculosis treatment [18]. Patients in arm C received antituberculosis treatment with a high dose of Rifampicin (15 mg/kg/day instead of 10 mg/kg/day) during the intensive phase of TB treatment followed by ARV therapy initiated two months after the antituberculosis treatment.

The duration of TB treatment was six months during which all the patients received a medical examination at each visit and performed blood tests for liver function assessment (ALT, AST, γ-GT, ALP, and total bilirubin). In all, the patients attended 10 visits scheduled as follows: first visit (Visit 1), one week before inclusion, second visit (Visit 2) on the day of inclusion, visits three to five (Visits 3-5); two, four, six weeks after inclusion and the remaining visits (Visits 6-10); three, four, five, and six months after inclusion.

Outcomes

The primary outcome was an elevation of ALT at least 5 times the Upper Limit of Normal (ULN) corresponding to Grade 3 ($5.0 \leq ALT < 10.0$ ULN) or 4 ($ALT \geq 10.0$ ULN) of the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.0, November 2014) [19].

The secondary outcomes were an isolated elevation Grade 4 of AST, γ-GT, ALP, and/or total bilirubin.

No case of treatment discontinuation has been recorded among the patients during the follow-up.

Statistical Analysis

The endpoints were analyzed per protocol. Quantitative variables were presented using means or medians with their standard deviation or interquartile range. The qualitative variables were presented as proportions. Statistical analyzes were performed with R software Version 4.1.0 and MedCalc software version 20.0.5.

The chi-square test and Fisher's exact test were used to compare the proportions two by two. The significance level of the tests was set at 5%.

Results and Discussion

Characteristics of Patients

A total of 780 patients were randomized into three treatment arms **(Table 2)**. They were 212 from Benin, 470 from Guinea, 98 from Senegal and 53.97 % (421 out of 780) were men, 2.44% (19 out of 780) co-infected with HBV or HCV.

Table 2. Demographic and clinical characteristics of patients at baseline

Characteristics	Randomization arms		
	A (n=263)	B (n=258)	C (n=259)
Sex			
Male	137 (51.0%)	146 (56.6%)	141 (54.4%)
Female	129 (49.0%)	112 (43.4%)	118 (45.6%)
Age (years)			
Means ± SD*	36.4 ± 9.2	36.5 ± 10.1	35.9 ±9.7
Ranges	18 - 60	19 - 69	18 - 67
BMI (kg/m^2)			
Means ± SD	18.2 ± 3.1	17.7 ± 2.9	18.4 ± 2.6
Ranges	11.1 - 28.9	12.4 - 27.2	12.1 - 27.1
Underweight	85 (63.9%)	87 (66.9%)	72 (57.6%)
Normal weight	43 (32.3%)	39 (30.0%)	47 (37.6%)
Overweight	5 (3.8%)	4 (3.1%)	6 (4.8%)
Hepatitis B or C			
Yes	8 (3.0%)	5 (1.9%)	6 (2.3%)
No	16 (6.1%)	18 (7.0%)	17 (6.6%)
Unkown	239 (90.9%)	235 (91.1%)	236 (91.1%)
Viral load (copies/ml)			
Medians	125,8	154,1	300
IQR	40 - 600	16.2 - 800	65 - 566
CD4 count (Cell/mm^3)			

Medians	174	175	187
IQR	99 - 288	108 - 269.3	114 - 312

n: Number of study participants, SD: Standard Deviation, ml: millimeter, CD4: Cluster of Differentiation 4, IQR: Interquartile range, BMI: Body Mass Index

From the additional statistical analysis performed, no confounding factors were identified among the demographic, co-medications, and comorbidities available variables

Few cases of Grade 4 toxicity for ALP and total bilirubin were identified among the patients at baseline **(Table 3)**.

Table 3. Liver testings of patients at baseline

Characteristics	Randomization arms		P-value
	B (n=258)	C (n=259)	
ALT			
Normal	243 (94.2%)	248 (95.8%)	0.4161
Grade 1	13 (5.0%)	11 (4.2%)	0.6826
Grade 2	2 (0.8%)	0 (0.0%)	0.2485
AST			
Normal	212 (82.2%)	219 (84.6%)	0.5035
Grade 1	40 (15.5%)	33 (12.7%)	0.735
Grade 2	6 (2.3%)	6 (2.3 %)	1.000
Grade 3	0 (0.0 %)	1 (0.4 %)	1.000
γ-GT			
Normal	155 (60.1%)	150 (57.9%)	0.6966
Grade 1	60 (23.3%)	67 (25.9%)	0.7354
Grade 2	26 (10.1%)	22 (8.5%)	0.8512
Grade 3	17 (6.6%)	20 (7.7%)	0.7334
ALP			
Normal	186 (72.1%)	177 (68.3%)	0.4292
Grade 1	47 (18.2%)	51 (19.7%)	0.8507
Grade 2	14 (5.4%)	21 (8.1%)	0.2935
Grade 3	10 (3.9%)	8 (3.1%)	0.6413
Grade 4	1 (0.4 %)	2 (0.8%)	1.000
Total bilirubin			
Normal	80 (31.0%)	74 (28.6%)	0.7458
Grade 1	37 (14.3%)	37 (14.3%)	1.000
Grade 2	10 (3.9%)	12 (4.6%)	0.8281
Grade 3	6 (2.3%)	8 (3.1%)	0.7876
Grade 4	125 (48.4%)	128 (49.4%)	0.8738

ALT: Alanine aminotransferase; ASAT: Aspartate aminotransferase; ɤ-GT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase

Hepatic Safety

During the patients' follow-up, there were no significant differences between the ALT mean values in the study arms **(Table 4)**.

Table 4. ALT results during patients follow-up

ALT	Randomization arms		P-values
	B (n=258)	C (n=259)	
Visit 3			
Normal	247 (95.7%)	242 (93.4%)	0.2323
Grade 1	10 (3.9%)	15 (5.8%)	0.4127
Grade 2	1 (0.4%)	2 (0.8%)	1.000
Visit 4			
Normal	245 (95.0%)	246 (95.0%)	1.000
Grade 1	12 (4.7%)	12 (4.6%)	1.000
Grade 2	1 (0.4 %)	1 (0.4%)	1.000
Visit 5			
Normal	243 (94.2%)	245 (94.6%)	0.8478
Grade 1	13 (5.0%)	13 (5.0%)	1.000
Grade 2	2 (0.8%)	1 (0.4%)	0.6235
Visit 6			
Normal	247 (95.7%)	246 (95.0%)	0.7123
Grade 1	9 (3.5%)	12 (4.6%)	0.6569
Grade 2	2 (0.8%)	1 (0.4%)	0.6235
Visit 10			
Normal	245 (95.0%)	240 (92.7%)	0.2919
Grade 1	12 (4.7%)	17 (6.6%)	0.4451
Grade 2	1 (0.4%)	2 (0.8%)	1.000

There were no significant differences between arms B and C patients during the follow-up at Visit 6.

The Grades 3 or 4 of γ-GT, ALP, and total bilirubin were more frequent within the study arms. However, there was no significant difference.

To the best of our knowledge, this study is the first conducted in the three West African countries to assess the hepatic tolerability of a high-dose Rifampicin antituberculosis regimen in TB/HIV co-infected patients. This was a randomized clinical trial with patients' characteristics at baseline well distributed among the three arms. The participants from Guinea were more represented probably due to the higher TB/HIV co-infection prevalence in the country [20]. The number of patients per country and gender ratio were identical for all the randomization arms.

The lymphocytes T CD4 count of the patients included in this study was between 50 and 350 cells/mm^3. These rates are compatible with high survival in TB/HIV co-infected patients. In addition, patients with a CD4 count < 50 have a higher risk of death requiring immediate start (during the first two weeks after diagnosis) of ART. They are also at risk for Immune Reconstitution Inflammatory Syndrome (IRIS) due to anti-TB treatment. On the other hand, in patients with T cells CD4 count of > 350, antiretroviral treatment may be postponed beyond two months. In the study by Petros *et al.*,

patients who had presented liver injury despite their average levels of CD4 count (69.3 ± 48.7 cells/mm^3) between 50 and 350 cells/mm^3 had the *HLA-B*57* (Human Leukocyte Antigen B subtype 57) phenotype [21]. It is therefore obvious that independently of the Rifampicin doses, an immuno-allergic mechanism would also contribute to the onset of liver injury induced by antituberculosis drugs.

Many other studies such as those of Milstein *et al.* and Boeree *et al.* confirmed in TB patients the safety and efficacy of different treatment regimens with high doses of Rifampicin ranging from 20 to 35 mg/kg/day [9, 11]. TB/HIV co-infection being a risk factor for liver injury, high dose Rifampicin regimens (From 20 to 35 mg/kg/day) are risky. In this study, the use of Rifampicin at the dose of 15 mg/kg/day was reasonable and safe for TB/HIV co-infected patients.

Patients in arm C had shown acute and mild toxicity that disappeared during the continuation phase of TB treatment. They did not show any significant increase in ɤ-GT and ALP after two months of treatment (Sixth visit). The increase in ɤ-GT and ALP is frequent in the first trimester of TB treatment. This is said to be the consequence of an immuno-allergic mechanism in which intensity varies from one patient to another [22].

Rare cases of hepatic toxicity corresponding to Grade 3 elevation in ALT had been recorded among patients in arm C. However, no case of toxicity had been recorded in patients in arm B (Reference arm). These were cases of transient toxicity that disappeared with the treatment continuation. However, there was no significant difference between the mean ALT values of the three randomization arms.

Concomitant treatment, low Body Mass Index (BMI), and oxidative stress are well-known risk factors of liver injury in TB/HIV co-infected patients [23, 24]. During the follow-up of the patients, no concomitant treatment had been recorded. Despite the risk of hepatotoxicity linked to BMI less than 18.5 kg/m^2, the patients in the three study arms did not present any serious signs of hepatotoxicity [25]. Oxidative stress was not assessed in this study. Its assessment would have made it possible to know the effects of anti-TB drugs and ARVs.

Among the first-line antituberculosis drugs, Isoniazid is the most hepatotoxic [26-30]. In this study, all patients received the same dose (5 mg/kg/day) that is only hepatotoxic for patients with a mutation of the N-Acetyltransferase 2 (*NAT2*), Glutathione S-Transferase (*GST*), or Cytochrome P4502E1 (*CYP2E1*) gene [30-33]. Some patients may have two or more mutations of these genes leading to a higher risk of liver injury. In order to secure the use of Isoniazid, it is important to determine the genotype of the patients before using the drug. Under treatment, it is also important to frequently check the levels of liver enzymes.

PZA could be hepatotoxic for TB patients co-infected by HCV or HIV. In 2020, two studies published by Oscanoa *et al.* and Kwon *et al.* have shown that liver toxicity induced by PZA is most frequent than thought [34, 35]. Therefore, the incidence of liver toxicity due to PZA seems to be underestimated as shown by the great number of publications ranking INH as the first liver toxic drug.

Apart from liver toxicity, there are other kinds of toxicities (kidney toxicity, blood toxicity, etc.) that could be assessed in order to improve TB treatment among TB/HIV co-infected patients.

Conclusion

This study showed that a high-dose Rifampicin regimen for TB treatment in TB/HIV co-infected patients was as safe as a standard regimen associated with late initiation of ARV therapy. There were no significant differences between the mean values of ALT, AST, γ-GT, ALP, and total bilirubin of the standard regimens and the Rifampicin high-dose regimen. However, a few cases of liver injury corresponding to Grade 3 or 4 of hepatic parameters elevations were recorded in the study arms.

Additional studies are needed to assess the renal and hematological safety of the high-dose Rifampicin regimen to ensure its safety.

Study protocol

Available in the supporting information and at dx.doi.org/10.17504/protocols.io.btipnkdn.

Trial registration

PACTR201105000291300, RAFA

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CONFLICT OF INTEREST: None

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ETHICS STATEMENT: The RAFA trial has been approved by the National Ethics Committees of Benin (Reference 004 31 March 2011), Guinea (Reference 02/CNERS/11) and Senegal (Reference 000117MSP/DS/CNERS).

References

1. World Health Organisation. Global Tuberculosis Report. Geneva: 2019. doi:10.16309/j.cnki.issn.1007-1776.2003.03.004.
2. Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89(6):806-15. doi:10.1038/clpt.2011.58.
3. Wang T, Lin S, Shie S, Chou P, Huang C, Chung F. Clinical Characteristics and Treatment Outcomes of Patients with Low- and High-Concentration Isoniazid- Monoresistant Tuberculosis. 2014;9(1):1-6. doi:10.1371/journal.pone.0086316.
4. Bao Y, Ma X, Rasmussen TP, Zhong XB. Genetic Variations Associated with Anti-Tuberculosis Drug-Induced Liver Injury. Curr Pharmacol Rep. 2018;4(3):171-81. doi:10.1007/s40495-018-0131-8.

5. Gurumurthy P, Ramachandran G, Kumar AKH, Rajasekaran S, Padmapriyadarsini C, Swaminathan S, et al. Decreased Bioavailability of Rifampin and Other Antituberculosis Drugs in Patients with Advanced Human Immunodeficiency Virus Disease. Society. 2004;48(11):4473-5. doi:10.1128/AAC.48.11.4473.
6. Chigutsa E, Visser ME, Swart EC, Denti P, Pushpakom S, Egan D, et al. The SLCO1B1 rs4149032 polymorphism is highly prevalent in South Africans and is associated with reduced rifampin concentrations: Dosing implications. Antimicrob Agents Chemother. 2011;55(9):4122-7. doi:10.1128/AAC.01833-10.
7. Gumbo T, Louie A, Deziel MR, Liu W, Parsons LM, Salfinger M, et al. Concentration-dependent Mycobacterium tuberculosis killing and prevention of resistance by rifampin. Antimicrob Agents Chemother. 2007;51(11):3781-8. doi:10.1128/AAC.01533-06.
8. Jindani A, Harrison TS, Nunn AJ, Phillips PPJ, Churchyard GJ, Charalambous S, et al. High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis. N Engl J Med. 2014;371:1599-608. doi:10.1056/NEJMoa1314210.
9. Ruslami R, Menzies D. Finding the right dose of rifampicin, and the right dose of optimism. Lancet Infect Dis. 2017;17(1):2-3. doi:10.1016/S1473-3099(16)30315-2.
10. Milstein M, Lecca L, Peloquin C, Mitchison D, Seung K, Pagano M, et al. Evaluation of high-dose rifampin in patients with new, smear-positive tuberculosis (HIRIF): Study protocol for a randomized controlled trial. BMC Infect Dis. 2016;16(1):1-7. doi:10.1186/s12879-016-1790-x.
11. Steingart KR, Jotblad S, Robsky K, Deck D, Hopewell PC, Huang D, et al. Higher-dose rifampin for the treatment of pulmonary tuberculosis: a systematic review [Review article]. Int J Tuberc Lung Dis. 2011;15(3):305-16.
12. Boeree MJ, Diacon AH, Dawson R, Narunsky K, Du Bois J, Venter A, 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(9):1058-65. doi:10.1164/rccm.201407-1264OC.
13. Ruslami R, Nijland HMJ, Alisjahbana B, Parwati I, Van Crevel R, Aarnoutse RE. Pharmacokinetics and tolerability of a higher rifampin dose versus the standard dose in pulmonary tuberculosis patients. Antimicrob Agents Chemother. 2007;51(7):2546-51. doi:10.1128/AAC.01550-06.
14. Boeree MJ, Van Balen GP, Aarnoutse RA. High-dose rifampicin: How do we proceed? Int J Tuberc Lung Dis. 2011;15(8):1133. doi:10.5588/ijtld.11.0198.
15. Hu Y, Liu A, Ortega-Muro F, Alameda-Martin L, Mitchison D, Coates A. High-dose rifampicin kills persisters, shortens treatment duration, and reduces relapse rate in vitro and in vivo. Front Microbiol. 2015;6:1-10. doi:10.3389/fmicb.2015.00641.
16. Boeree MJ, Heinrich N, Aarnoutse R, Diacon AH, Dawson R, Rehal S, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. Lancet Infect Dis. 2017;17(1):39-49. doi:10.1016/S1473-3099(16)30274-2.
17. Onorato L, Gentile V, Russo A, Caprio G Di, Alessio L, Chiodini P, et al. Standard versus high dose of rifampicin in the treatment of pulmonary tuberculosis : a systematic review and meta-analysis. Clin Microbiol Infect. 2021;27(6):830-7.
18. World Health Organization. Treatment of Tuberculosis Guidelines. Geneva: 2009.
19. National Institute of Allergy and Infectious Diseases. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. 2014. doi:10.7326/0003-4819-157-11-201212040-00003.
20. WHO. Global Tuberculosis Report 2016. Geneva: 2016. doi:ISBN 978 92 4 156539 4.
21. Petros Z, Kishikawa J, Makonnen E, Yimer G, Habtewold A, Aklillu E. HLA-B*57 allele is associated with concomitant anti-tuberculosis and antiretroviral drugs induced liver toxicity in ethiopians. Front Pharmacol. 2017;8:1-9. doi:10.3389/fphar.2017.00090.
22. Walker L, Yip V, Pirmohamed M. Adverse Drug Reactions. Elsevier Inc.; 2014. doi:10.1016/B978-0-12-386882-4.00020-7.
23. Hassen Ali A, Belachew T, Yami A, Ayen WY. Anti-Tuberculosis Drug Induced Hepatotoxicity among TB/HIV Co-Infected Patients at Jimma University Hospital, Ethiopia: Nested Case-Control Study. PLoS One. 2013;8(5):e64622. doi:10.1371/journal.pone.0064622.
24. Björnsson ES. Hepatotoxicity by drugs: The most common implicated agents. Int J Mol Sci. 2016;17(2):224. doi:10.3390/ijms17020224.
25. Sarges P, Steinberg JM, Lewis JH. Drug-Induced Liver Injury: Highlights from a Review of the 2015 Literature. Drug Saf. 2016;39(9):801-21. doi:10.1007/s40264-016-0427-8.
26. Björnsson ES. Drug-induced liver injury: an overview over the most critical compounds. Arch Toxicol. 2015;89(3):327-34. doi:10.1007/s00204-015-1456-2.
27. Wang P, Pradhan K, Zhong XB, Ma X. Isoniazid metabolism and hepatotoxicity. Acta Pharm Sin B. 2016;6(5):384-92. doi:10.1016/j.apsb.2016.07.014.
28. Metushi I, Uetrecht J, Phillips E. Mechanism of isoniazid-induced hepatotoxicity: Then and now. Br J Clin Pharmacol. 2016;81(6):1030-6. doi:10.1111/bcp.12885.
29. Daly AK, Martin Armstrong MP. Pharmacogenetics of Adverse Drug Reactions. Pharmacogenetics Individ. Ther. First Edit, John Wiley & Sons, Inc; 2012. p. 295-321. doi:10.1016/bs.apha.2018.03.002.
30. Kim SH, Kim SH, Lee JH, Lee BH, Kim YS, Park JS, et al. Polymorphisms in drug transporter genes (ABCB1, SLCO1B1 and ABCC2) and hepatitis induced by antituberculosis drugs. Tuberculosis. 2012;92(1):100-4. doi:10.1016/j.tube.2011.09.007.
31. Andrade R, Agundez J, Lucena M, Martinez C, Cueto R, Garcia-Martin E. Pharmacogenomics in Drug Induced Liver Injury. Curr Drug Metab. 2009;10(9):956-70. doi:10.2174/138920009790711805.
32. Yew WW, Chang KC, Chan DP. Oxidative Stress and First-Line Antituberculosis Drug-Induced Hepatotoxicity. Antimicrob Agents Chemother. 2018;62(8):1-11.
33. Oscanoa T, Moscol S, Amado J. Clinical characteristics of pyrazinamide-associated hepatotoxicity in patients at a hospital in lima, peru. Rev Peru Med Exp Salud Publica. 2020;37(3):516-20.
34. Kwon BS, Kim Y, Lee SH, Lim SY, Lee YJ, Park JS, et al. The high incidence of severe adverse events due to pyrazinamide in elderly patients with tuberculosis. PLoS One. 2020;15(7 July):1-10.
35. Waggiallah HA, Eltayeb LB, BinShaya AS, Elmahi OM. A saga of Hepcidin anti-microbial Effectiveness as Iron Acquisitor and Anemia Initiator in Mycobacterium Tuberculosis Infection. J Biochem Techol. 2020;11(2):128-34.