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Assessment of selected liver enzyme activity in patients with rifampicin-resistant tuberculosis receiving treatment at a tertiary healthcare facility, southwest Nigeria

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Abstract:

Background: Several anti-tuberculous drugs have been effective in the treatment and management of drug-sensitive and -resistant tuberculosis (TB). While these drug combinations have proven to be highly active against tubercle bacilli, side effects and toxicity may occur with tendency to interrupt or discontinue therapy, resulting in poor compliance. The objective of this study is to assess hepatotoxic potentials of anti-TB drugs among patients with rifampicin-resistant TB (RRTB) undergoing treatment at the directly observed treatment short-course (DOTS) clinic of Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital, Ogbomoso, Nigeria.

Methodology: This was a prospective study of 40 patients with RRTB on second-line anti-TB therapy including bedaquiline, moxifloxacin, prothionamide, ethambutol, pyrazinamide, isoniazid and clofazimine. RRTB was diagnosed by sputum smear AFB microscopy and Xpert MTB/RIF assay at the TB laboratory of Bowen University Teaching Hospital, Ogbomoso, Nigeria. Forty gender and age-matched apparently healthy persons were used as control. Venous samples (~5ml) were collected from each participant at baseline (prior to commencement of anti-TB therapy) and after completion of 9-11 months therapy, as well as from the controls. Plasma was separated by centrifugation and the activity of ALT, AST and ALP was measured by spectrophotometric analysis, while total protein and albumin levels were determined using routine methods. Data were presented as mean±SD and analysed using SPSS version 21.0. Comparison of the mean enzyme activity at baseline and after completion of therapy as well as with the control was done with unpaired 't' test, and 'p' (two tail) value less than 0.05 was considered statistically significant.

Results: The age range of the 40 RRTB patients is 20-67 years (mean age 45.50±10.1 years) while the age range of the 40 controls is 21-65 years (mean age 45.70±12.10 years). The male to female ratio is 1.2:1 for the patients and 1:1 for the control. There is statistically significant increase in post-therapy plasma activity of ALT ($p<0.0001$), AST ($p<0.0001$), ALP ($p<0.0001$), and total protein level ($p=0.0086$) compared to the baseline, while plasma albumin level decreased significantly post-therapy ($p=0.007$). Although there is no significant difference in the baseline activity of ALT ($p=0.4936$) and AST ($p=0.2539$) for the RRTB patients compared to the control, post-treatment activity of ALT ($p<0.0001$) and AST ($p<0.0001$) in RRTB patients were significantly higher than in apparently heathy controls.

Conclusion: The activity of the liver enzymes (AST and ALT) reported among RRTB patients in our study are within the normal reference range for persons above 18 years of age, indicating a non-hepatotoxic effect of the anti-TB drugs. However, statistically significant increase in these enzyme activities in the patients' post-treatment compared to the baseline, and to apparently healthy controls, indicates that the drugs may be potentially hepatotoxic on prolonged usage.

Keywords: rifampicin resistant tuberculosis; anti-TB drugs; ALT; AST; ALP; hepatotoxicity

Évaluation de l'activité des enzymes hépatiques sélectionnées chez les patients atteints de tuberculose résistante à la rifampicine recevant un traitement dans un établissement de soins de santé tertiaires, dans le sud-ouest du Nigeria

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Résumé:

Contexte: Plusieurs médicaments antituberculeux se sont révélés efficaces dans le traitement et la prise en charge de la tuberculose pharmacosensible et résistante. Bien que ces combinaisons de médicaments se soient avérées très actives contre les bacilles tuberculeux, des effets secondaires et une toxicité peuvent survenir avec une tendance à interrompre ou à interrompre le traitement, entraînant une mauvaise observance. L'objectif de cette étude est d'évaluer les potentiels hépatotoxiques des médicaments antituberculeux chez les patients atteints de tuberculose résistante à la rifampicine (RRTB) qui suivent un traitement à la clinique DOTS (Traitement de courte durée directement observé) de l'Université de technologie de Ladoke Akintola (LAUTECH), Hôpital, Ogbomoso, Ogbomoso

Méthodologie: Il s'agissait d'une étude prospective de 40 patients atteints de RRTB sous traitement antituberculeux de deuxième ligne comprenant la bédaquiline, la moxifloxacine, le prothionamide, l'éthambutol, le pyrazinamide, l'isoniazide et la clofazimine. La RRTB a été diagnostiquée par microscopie AFB des frottis d'expectoration et test Xpert MTB/RIF au laboratoire de la tuberculose de l'hôpital universitaire de Bowen, à Ogbomoso, au Nigeria. Quarante personnes apparemment en bonne santé appariées selon le sexe et l'âge ont été utilisées comme contrôle. Des échantillons veineux (~5ml) ont été prélevés sur chaque participant au départ (avant le début du traitement antituberculeux) et après la fin du traitement de 9 à 11 mois, ainsi que sur les témoins. Le plasma a été séparé par centrifugation et l'activité de l'ALT, de l'AST et de l'ALP a été mesurée par analyse spectrophotométrique, tandis que les taux de protéines totales et d'albumine ont été déterminés à l'aide de méthodes de routine. Les données ont été présentées sous forme de moyenne ± ET et analysées à l'aide de SPSS version 21.0. La comparaison de l'activité enzymatique moyenne au départ et après la fin du traitement ainsi qu'avec le contrôle a été effectuée avec un test «*t*» non apparié, et une valeur «*p*» (deux queues) inférieure à 0,05 a été considérée comme statistiquement significative.

Résultats: La tranche d'âge des 40 patients RRTB est de 20 à 67 ans (âge moyen 45,50±10,1 ans) tandis que la tranche d'âge des 40 témoins est de 21 à 65 ans (âge moyen 45,70±12,10 ans). Le ratio hommes/femmes est 1.2:1 pour les patients et 1:1 pour le contrôle. Il y a une augmentation statistiquement significative de l'activité plasmatique post-thérapie de l'ALT ($p<0,0001$), de l'AST ($p<0,0001$), de l'ALP ($p<0,0001$) et du taux de protéines totales ($p=0,0086$) par rapport à la ligne de base, tandis que l'albumine plasmatique le niveau a diminué significativement après le traitement ($p=0,007$). Bien qu'il n'y ait pas de différence significative dans l'activité de base de l'ALT ($p=0,4936$) et de l'AST ($p=0,2539$) pour les patients atteints de RRTB par rapport au groupe témoin, l'activité post-traitement de l'ALT ($p<0,0001$) et de l'AST ($p<0,0001$) chez les patients RRTB étaient significativement plus élevés que chez les témoins apparemment en bonne santé.

Conclusion: L'activité des enzymes hépatiques (AST et ALT) rapportée chez les patients atteints de RRTB dans notre étude se situe dans la plage de référence normale pour les personnes de plus de 18 ans, indiquant un effet non hépatotoxique des médicaments antituberculeux. Cependant, une augmentation statistiquement significative de ces activités enzymatiques chez les patients après le traitement par rapport à la ligne de base et à des témoins apparemment sains, indique que les médicaments peuvent être potentiellement hépatotoxiques en cas d'utilisation prolongée.

Mots clés: tuberculose résistante à la rifampicine; médicaments antituberculeux; ALT; AST; ALP; hépatotoxicité

Introduction:

Tuberculosis remains a global public health concern, and a leading cause of death worldwide, particularly in developing countries (1). The causative pathogen, which are members of the *Mycobacterium tuberculosis* complex (MTBC), primarily affects the lungs causing pulmonary TB, but can also affect other organs outside the lungs (extra-pulmonary TB). Members of MTBC include *Mycobacterium tuberculosis*, *Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti,* and *Mycobacterium canetti* (2). The burden of TB remains high globally with an estimated 10 million new cases and 1.5 million TB-related deaths in 2019 (3), however, case detection rate is only about 64%, with estimated 36% undetected. Nigeria is ranked seventh among the 30 high-TB burden countries and second in Africa, with an estimated 407,000 TB cases and 154,000 deaths per year (4). Management of TB has been made worse in Nigeria by issues of drug resistance, HIV/AIDS epidemic, and low treatment coverage resulting from low TB case finding for both adults and children (5).

The first line drugs for the treatment of drug-sensitive TB includes rifampicin, pyrazinamide, ethambutol, and isoniazid, while second line drugs are reserved for drug resistant TB, and includes drugs in different classes such as fluoroquinolones (levofloxacin, moxifloxacin, gatifloxacin), linezolid, cycloserine, bedaquiline, delamanid, imipenem, ethionamide, para-amino salicylic acid, clofazimine, injectable aminoglycosides among others (6). There has however been increase

in resistance of tubercle bacilli to these drugs (7) with emergence of multi-drug resistant (MDR) strains.

Multidrug resistance is defined as resistance to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs, and is classified into two categories; resistance to only isoniazid and rifampicin, known as basic MDR-TB, and resistance to these two drugs, in addition to one or more first and/or second-line drugs, categorized as MDR-TB-plus (8). Rifampicin resistant TB (RRTB) is defined by the World Health Organization (WHO) as any resistance to rifampicin including mono-resistance, multidrug resistance, extensively drug resistance and pandrug resistance (6). When compared to first-line treatment, RRTB treatment is generally extended and involves the use of less effective drug regimens with more adverse effects (9). In a systematic review and meta-analysis of prevalence of TB in Nigeria, Oyedum and his colleagues (10) reported resistant rates to any TB drug among new and previously treated TB cases of 32% and 53%, and MDR rates of 6% and 32% respectively.

Minor adverse effects of second-line anti-TB drugs are quite common but can be easily managed. However, some adverse effects such as nephrotoxicity from injectable aminoglycosides, cardiotoxicity from fluoroquinolones, hepatic, intestinal, and central nervous toxicity, can be life-threatening (11). Liver enzymes such as alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) are commonly used to assess liver functions and determine hepatocellular damage. Hepatotoxicity has been associated with an increase in serum ALT and AST greater than three times of upper limit of reference (ULR). The objective of this prospective study is to assess the potential risk of drug-induced liver injury in a cohort of patients with RRTB on second-line anti-TB drugs at the DOTS clinic of LAUTECH Teaching Hospital, Ogbomoso, Nigeria, by assay of plasma activity of ALT, AST and ALP as well as serum levels of total protein and albumin in these patients (pre-and post-treatment), and comparing these with those from apparently healthy individuals.

Materials and method:

Study setting

This study was carried out at the directly observed treatment short-course (DOTS) clinic of Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital, Ogbomoso, Oyo State, southwest Nigeria. The State has an estimated population of 5,580,894 (12) and a land mass of 28,454 square kilometers with an equatorial climate of dry and wet seasons of relatively high humidity. Ogbomoso is the second largest city in Oyo State.

Study design and subject participants

This was a prospective study of 40 rifampicin-resistant TB (RRTB) patients on second line anti-TB therapy for a duration of 9-11 months (depending on compliance and sputum conversion) who were randomly selected among TB patients attending the DOTS clinic or hospitalized between January 2019 and July 2021. The second line drugs used included WHO approved combination regimen for RRTB (13), with bedaquiline, clofazimine, prothionamide, pyrazinamide, ethambutol and high-dose isoniazid for the intensive phase of 6 months followed by moxifloxacin, clofazimine, pyrazinamide and ethambutol for the continuation phase of 5 months. Forty apparently healthy adults were randomly recruited among voluntary blood donors within the period of the study to serve as control.

Ethical approval

Ethical approval was obtained from the Ethical Review committee of LAUTECH Teaching Hospital. Written informed consent was obtained from all participants and confidentiality of data was assured.

Inclusion and exclusion criteria

The criteria for inclusion in the study were; (i) written informed consent of participants, (ii) fulfilment of clinical and laboratory criteria for diagnosis of RRTB based on radiological evidence of TB, sputum smear positive for AFB on Ziehl-Neelsen (ZN) stain, and positive Xpert MTB/RIF assay, and (iii) willingness to comply with anti-TB treatment regimen. Exclusion criteria were patients already on second line anti-TB drugs before recruitment, pregnancy, co-infection with HIV, patients with features of acute and chronic liver diseases, and patients positive for hepatitis B and C viruses.

Data and samples collection

Baseline demographic data (age and gender) of each selected participant were collected into a designed data collection form before commencement of second line anti-TB drugs. Sputum samples (~10 ml) were collected into sterile universal bottles from each study participant according to the DOTS method of spot, morning and spot (SMS) protocol for the purpose of AFB microscopy by ZN stain and Xpert MTB/RIF assay. Approximately 5ml of venous blood were also collected from each patient and control into ethylene diamine tetra-acetic acid (EDTA) specimen bottles for liver enzyme analysis. At the completion of anti-TB therapy, another

5ml of blood samples were collected from the patient to measure the activity of the liver enzymes.

Sample processing and enzyme activity measurement

Microscopic examination for AFB by ZN stain was carried out by two trained medical laboratory scientists. Only concordant positive results were considered in line with WHO criteria for smear positive TB (14). RRTB was detected by Xpert MTB/RIF assay at the TB laboratory of Bowen University Teaching Hospital, Ogbomoso, Nigeria.

AST activity (measured in IU/L) was assayed by spectrophotometric measurement of the concentration of oxaloacetate hydrazone formed with 2,4-dinitrophenyldrazine while ALT activity was determined by measuring the concentration of pyruvate hydrazone formed with 2,4-dinitro phenyldrazine according to Reitman and Frankel (15), using analytical grade commercial reagents (Randox Laboratories Limited, United Kingdom) that can assay between 7 to 89 IU/L and 4 to 94 IU/L activity of AST and ALT respectively. ALP activity was determined by measuring the concentration of chromogen formed from the enzyme activity on 2-amino-2-methyl-1-propanol-buffered sodium thymolphthalein monophosphate with commercial assay kit (Teco Diagnostics, Anaheim, USA) that has detection limits of 1 to 100 IU/L. Total plasma protein was estimated using Biuret method (16) while plasma albumin was measured by the routine method of Tietz (17).

Statistical analysis

Data were presented as mean±SD and analysed with the Statistical Package for the Social Sciences (SPSS) version 21.0. Difference in mean values of enzyme activity between pre- and post-TB treatment, and with apparently healthy control was determined using unpaired '*t*' test and '*p*' value (two-tail) less than 0.05 was considered as statistically significant.

Results:

A total of 40 rifampicin-resistant TB patients (age range 20-67 years, mean age 45.50±10.1 years) and 40 gender and age-matched apparently healthy individuals (age range 21-65 years, mean age 45.70 ±12.10 years) were enrolled for the study (Table 1). The male to female ratio in the patients is 1.2:1 while the male to female ratio in the controls is 1:1.

Table 2 is a comparison of liver parameters pre- and post-TB therapy which showed statistically significant increase in post-therapy plasma activity of ALT (95% CI = 2.439-5.361, *p*<0.0001), AST (95% CI = 7.471-10.729, *p*<0.0001) and ALP (95% CI =2.846-7.354, *p*<0.0001) over the baseline values. The plasma total protein level was also significantly higher post-therapy (95% CI=1.463 to 9.637, *p*=0.0086), while plasma albumin level decreased significantly post-therapy (95% CI= -6.69 to -1.11, *p*=0.007).

Table 3 is a comparison of liver enzyme activity of patients with RRTB at baseline (prior to anti-TB therapy commencement) with apparently healthy controls, which showed that there is no significant difference in the baseline activity of ALT (95% CI = -0.569 to +1.169, *p*=0.4936) and AST (95% CI = -0.659 to +2.459, *p*=0.2539) of the patients and the control, but ALP activity was significantly higher in the control than baseline activity in RRTB patients (95% CI=3.936 to 7.864, *p* <0.0001).

Table 4 is a comparison of liver enzyme activity of patients with RRTB post-treatment with apparently healthy controls, which showed that post-treatment ALT (95% CI = 2.126 to 5.074, *p*<0.0001) and AST (95% CI= 6.520 to 9.871, *p*<0.0001) activity were significantly higher in RRTB patients' than apparently heathy controls, but no significant difference in the activity of ALP between the two groups (95% CI = -2.937 to 1.337, *p*=0.4579)

Table 1: Gender and age distribution of selected patients with rifampicin resistant tuberculosis and apparently healthy controls in LAUTECH Teaching Hospital, Ogbomoso, Nigeria

Demographic variable	RRTB patient (n=40)		Apparently healthy control (n=40)	
Age groups (years)	Male	Female	Male	Female
20-29	2	2	2	2
30-39	2	3	5	4
40-49	9	8	2	7
50-59	7	3	6	5
≥60	2	2	5	2
Total	**22**	**18**	**20**	**20**
Mean age	45.50 ± 10.1		45.70 ±12.10	
Age range	20 – 67		21 – 65	
Male: Female ratio	1.2: 1		1: 1	

RRTB = rifampicin resistant tuberculosis; n=number

Table 2: Comparison of liver parameters before and after anti-tuberculous treatment in patients with rifampicin-resistant tuberculosis in LAUTECH Teaching Hospital, Ogbomoso, Nigeria

Liver parameters	Values at baseline (mean±SD)	Values post-treatment (mean±SD)	95% CI	p value
Alkaline phosphatase (IU/L)	15.1 ± 4.7	20.2 ± 5.4	2.846 to 7.354	<0.0001*
Aspartate transaminase (IU/L)	7.5 ±3.4	16.6 ± 3.9	7.471 to 10.728	<0.0001*
Alanine transaminase (IU/L)	4.70 ±1.9	8.6 ±4.2	2.439 to 5.361	<0.0001*
Total protein (g/dL)	71.25±6.80	76.8±11.01	1.463 to 9.637	0.0086*
Albumin (g/dL)	42.1±3.78	38.2±7.95	-6.689 to -1.111	0.0070*

*p value (two-tail) < 0.05 was taken as statistically significant; reference range: ALP 30-120 IU/L; AST 0-35 IU/L; ALT 0-45 IU/L; total protein 60-83 g/dL; albumin 35-50 g/dL; SD = standard deviation; CI = confidence interval

Table 3: Comparison of liver enzyme activity of patients with rifampicin resistant tuberculosis at baseline with apparently healthy controls in LAUTECH Teaching Hospital, Ogbomoso, Nigeria

Liver enzyme activity	Values at baseline (mean± SD)	Values in healthy controls (mean ±SD)	95% CI	p value
Alkaline phosphatase (IU/L)	15.1 ± 4.7	21.00 ±04.10	3.936 to 7.864	<0.0001*
Aspartate transaminase (IU/L)	7.5 ±3.4	08.40 ± 03.60	-0.6590 to +2.459	0.2539
Alanine transaminase (IU/L)	4.70 ±1.9	05.00 ±02.00	-0.5685 to +1.169	0.4936

*p value (two-tail) < 0.05 was taken as statistically significant; reference range: ALP 30-120 IU/L; AST 0-35 IU/L; ALT 0-45 IU/L; SD = standard deviation; CI = confidence interval

Table 4: Comparison of liver enzyme activity of patients with rifampicin resistant tuberculosis post-treatment with apparently healthy controls in LAUTECH Teaching Hospital, Ogbomoso, Nigeria

Liver enzyme activity	Values post treatment (mean± SD)	Values in healthy controls (mean ±SD)	95% CI	p value
Alkaline phosphatase (IU/L)	20.2 ± 5.4	21.00 ±04.10	-2.937 to 1.337	0.4579
Aspartate transaminase (IU/L)	16.6 ± 3.9	08.40 ± 03.60	6.529 to 9.871	<0.0001*
Alanine transaminase (IU/L)	8.6 ±4.2	05.00 ±02.00	2.126 to 5.074	<0.0001*

*p value (two-tail) < 0.05 was taken as statistically significant; reference range: ALP 30-120 IU/L; AST 0-35 IU/L; ALT 0-45 IU/L; SD = Standard deviation; CI = confidence interval

Discussion:

The mean age of the patients with tuberculosis in our study falls within the age group reported by Dharmik and his collea-gues (18), who ascribed the high prevalence of TB in this age group to increased physical activity, exposure and socio-economic factors as predisposing factors to the disease. Glo-bally, MDRTB/RRTB is rapidly becoming a major concern in the care, treatment and management of TB, which have emerged through inappropriate use of first line anti-TB drugs especially isoniazid, rifampicin and ethambutol. Meanwhile, anti-TB drug-induced hepatocellular injury have been widely repor-ted (18,19,20,21), and Enoh et al., (21) reported hepatotoxicity to be more prevalent in patients over 40 years of age. Adverse effects of drugs could alter treatment and results in poor outcomes from poor compli-ance with therapy. Our study revealed that plasma activity of aminotransferases (AST and ALT) increased significantly among RRTB patients after treatment with the standard second line anti-TB (bedaquiline, isoniazid, levofloxacin, linezolid and clofazimine) used

in our center, which agree with the study of Mirlohi et al., (20) that reported increased activity of AST and ALT among MDR-TB patients on anti-TB drugs.

Hepatotoxicity is usually associated with increased enzyme activity three times of upper limit of reference (ULR), even as reference values provide the basis for inter-pretations of results in clinical laboratory. As the reference range for AST and ALT activity is 0-35 IU/L and 0-45 IU/L respectively for individuals above 18 years of age (22), the enzyme activity in our study did not confirm hepatotoxicity in the patients as the enzyme activity were within normal reference range and not up to three times of ULR. However, statistically significant increase in enzyme activity in the patients' post-treatment when compared with the baseline and to the activity in apparently healthy controls, indi-cates that the drugs may be potentially hepatotoxic on prolonged usage. This is supported by the finding of significantly decreased albumin level post-therapy com-pared to baseline, which indicate that synthe-tic function of the liver may be potentially affected by the drugs

On the other hand, ALP has widespread tissue distribution including liver, bone, placenta and gastrointestinal tract, and its activity level have been found useful as a marker of hepatic cholestasis (23), but less useful as a marker of hepatocellular injury. In our study, ALP activity was also within the normal reference range (30-120 IU/L) pre- and post-TB therapy. Infact, the activity was significantly higher in healthy controls compared to RRTB patients at baseline, while there was no significant difference in the activity between RRTB patients' post-therapy and the controls.

Conclusion:

Our study showed the activity of liver enzymes (AST, ALT and ALP) in RRTB patients on second-line anti-TB drugs to be within the normal reference range for individuals above 18 years of age, indicating a non-toxic effect of these anti-TB drugs on the liver. However, statistically significant increase in post-treatment activity of AST and ALT, and significant decrease in albumin level in our patients compared to their baseline levels is an indication that the drugs may be potentially hepatotoxic on prolonged usage. We therefore recommend short term treatment regimen for RRTB patients, and close monitoring of hepatic functions of the patients during therapy. Further study will be required to evaluate hepatoxic potential of each of the second line anti-TB drugs.

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Authors' contributions:

OOA, OAK and AAA were involved in the study design, data collection, literature review, and manuscript draft preparation; OJO, ZTO, ATW, OAM and OAM were involved in data collection and literature review; and TSS was involved in critical review and correction of the draft manuscript and statistical analysis. All authors read and agreed with the final manuscript submitted.

Conflict of interest:

No conflict of interest is declared

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