International Journal of TROPICAL DISEASE & Health
10(1): 1-6, 2015, Article no.IJTDH.19448
ISSN: 2278–1005

SCIENCEDOMAIN *international*
www.sciencedomain.org

Antituberculosis Drug - Induced Elevation in Serum Alanine Aminotransferase (ALT) Levels: A Comparison between Patients with and without HIV Seropositivity in Yenagoa, Nigeria

Peter Ogie Ikuabe[1*], J. Jumbo[1], I. D. Ebuenyi[2], D. Ogoina[1] and T. C. Harry[1]

[1]Department of Internal Medicine, Niger Delta University Teaching Hospital, Okolobiri, Nigeria.
[2]Department of Community Medicine, Niger Delta University Teaching Hospital, Okolobiri, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. Author POI did the study design and wrote the protocol. Authors JJ and IDE did the statistical analysis and literature searches while analyses of study was by authors DO and TCH. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2015/19448
Editor(s):
(1) Thomas I. Nathaniel, Department of Biomedical Sciences, School of Medicine –Greenville, University of South Carolina, Greenville, USA.
Reviewers:
(1) Kadima Ntokamunda Justin, University of Rwanda, Rwanda.
(2) Mathew Folaranmi Olaniyan, Department of Medical Laboratory Sciences, Achievers University, Owo, Nigeria.
Complete Peer review History: http://sciencedomain.org/review-history/10105

Original Research Article

Received 10th June 2015
Accepted 23rd June 2015
Published 8th July 2015

ABSTRACT

Introduction: The prevalence of rifampicin, isoniazid and pyrazinamide induced elevations in serum alanine aminotransferase (ALT) levels were compared in a cohort of Nigerians with and without HIV seropositivity.
Methods: Records of all the patients with pulmonary tuberculosis (251 HIV positive and 205 HIV negative), aged above 15 years treated in the TB program of the Federal Medical Centre, Yenagoa from January 2013 to December 2014 were analysed for this study. The WHO 4 grades of hepatotoxicity using ALT were used. ALT of less than 50 U/L was taken as normal. Grade 1 (very mild hepatotoxicity): <2.5 x upper limit of normal (ULN) i.e. ALT 51-125 U/L. Grade 2 (mild): 2.6 – 5 x the ULN (ALT 126-250 U/L). Grade 3 (moderate): 5-10 x the ULN (ALT 251 – 500 U/L). Grade 4 (severe) >10 x the ULN (ALT > 500 U/L).
Results: No patient with or without HIV seropositivity had ALT value in the grade 3 and 4 category

**Corresponding author: Email: peterikuabe@yahoo.com;*

≥251 U/L. There was no statistically significant difference in ALT values between cohorts with or without HIV in the 3 ALT categories obtained while on antituberculous drugs (P = 0.761, 0.367 and 0.197).

Conclusion: All the observed hepatotoxicity were mild. The average rate of hepatotoxicity in the HIV uninfected pulmonary tuberculosis cohort was 16.6%, 9.8% and 5.4% for ALT_1, ALT_2 and ALT_3 respectively. The rate in the HIV infected cohorts was 15.5%, 8.8% and 16.4% for ALT_1, ALT_2 and ALT_3. It is encouraging to find a low rate of antituberculosis drug induced hepatotoxicity than one would expect based on the high prevalence of risk factors in our environment.

Keywords: Tuberculosis; antituberculosis drugs; HIV; HAART; alanine aminotransferase (ALT).

1. BACKGROUND

It has been reported that the response to antituberculosis (TB) treatment among HIV co-infected patients is generally good, though many require concurrent highly active antiretroviral therapy (HAART) to achieve a successful long term outcome [1,2]. It has also been reported that HIV/TB co-infected patients experience a higher rate of adverse drug reactions to treatment than those without HIV [3].

However, active TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in HIV infected patients should follow the general principles for individual without HIV. Treatment of drug susceptible TB disease should include a standard regimen that consists of first-line drugs-isoniazid, rifampicin, pyrazinamide and ethambutol given for 2 months, followed by isoniazid and rifampicin/ethambutol for 4 to 6 months [1-3]. All HIV positive patients with active TB disease should start antiretroviral treatment (ART). However, in patients with HIV-related tuberculosis, treating tuberculosis is the first priority [2]. In the setting of advanced HIV infection, untreated tuberculosis can progress rapidly to death. Anti-retroviral treatment may be lifesaving for patients with advanced HIV infection. Consequently, concurrent treatment may be necessary in patients with advance HIV disease (e.g circulating CD4 lymphocytes count < 200/UL). The newest policy guidelines from WHO recommends that ART should be given to all TB/HIV co-infected patients, irrespective of their CD4 cell count (and to all people living with HIV/AIDS with a CD4 cell count less than 500). The concominant use of anti-TB and antiretroviral (ARV) drugs is complicated by adherence challenge of pill burden, drug-drug interaction, overlapping adverse effects which is one of the serious adverse effect [2,4,5,6].

Anti TB drug induced hepatotoxicity is one of the most challenging problems and main cause of treatment interruption during TB treatment course that causes hospitalization and life-threatening events in other spheres [6-8]. Among the first line anti-TB drugs pyrazinanide, isoniazid and rifampicin have been associated with hepatotoxicity and the risk is enhanced when the drugs are used in combination [9]. Prevalence rate of hepatotoxicity in TB patients on treatment in different studies have varied from 1-31% [10-14]. The National Tuberculosis and Leprosy Control Programme (NTBLCP) recommends efavirenz based (Tenofovir, Lamivudine and Efavirenz) HAART regimen in all HIV-positive TB patients to reduce drug interactions with rifampicin [2].

We sought to compare anti-tuberculosis drug induced elevation in ALT between patients with and without HIV seroposivitiy in our patients since ALT is the most commonly used marker for liver injury. Although ALT is produced by other organs it is found predominantly in hepatocytes and is considered a specific marker for liver injury [15].

2. METHODS

2.1 Design

A retrospective cohort analysis of all collected medical records of adults (>15 years) patients seen in the ART/TB clinic of the Federal Medical Centre, Yenagoa between January 2013 and December 2014 was carried out using a standardized data extraction form. The demographic, clinical and laboratory parameters of patients were retrieved and analysed and these included smear status of AFB, chest radiograph where necessary, ALT_1 at baseline, ALT_2 at 4 weeks and ALT_3 at 8 weeks after commencement of anti-tuberculosis drugs. Those patients that had completed anti-tuberculosis drugs were excluded.

2.2 Setting

The study was undertaken in Federal Medical Centre, Yenagoa a Tertiary referral hospital in Bayelsa State, South-South, Nigeria. The HIV/AIDS treatment centre, situated within the hospital premises and supported by USAID/FHI 360 and NTBLCP, offers comprehensive HIV treatment and care to such patients free of charge. They also provide drugs free of charge to patients with pulmonary tuberculosis.

2.3 Diagnosis

The diagnosis of HIV/AIDS was based on WHO guidelines [16,17]. The diagnosis of pulmonary tuberculosis (PTB) required positive sputum acid fast bacilli or compatible clinical features and suggestive chest radiograph findings. Alanine aminotransferase (ALT) measurement was done with automatic biochemistry analyser (Horiba Medical, France). Human immunodeficiency virus (HIV) test was done by two serial testing using rapid test kit (Determine, Abbot Laboratories, UK) and confirmed by Western blot technique (Immunetica Qualicole, USA).

2.4 Statistical Analysis

The data were analysed using the EPI-INFO 2012 statistical program version 7.0.9.34. Continuous variables were described with mean and standard deviation, while discontinuous variables were described with proportions/rates. Rate means the ratio of patients in a category to the total number of patients in percentage. The Mann-Whitney test was used when comparing groups of cohort. At 95% confidence limit P-value less than or equal to 0.05 were considered to be significant.

2.5 Ethics Statement

Approval for conducting the study was obtained from the hospital Ethics committee. Patient consent was not obtained due to the retrospective nature of the study and any personally identifiable information was not collected and made available to maintain confidentiality.

3. RESULTS

A total of 470 adults pulmonary tuberculosis patients were attended to in the period under review. Of this number 6 deaths were recorded for reasons other than possible drug-induced hepatotoxicity, while 5 patients defaulted and 3 patients were transferred out. These 14 patients were excluded from the study. The rest 456 patients consisted of 251 HIV positive and 205 HIV negative individuals. Table 1 shows the characteristics of the patients.

Antituberculosis drug induced elevation in ALT: A comparison between patients with and without HIV sero-positivity.

For all the 3 groups (ALT_1, ALT_2 & ALT_3) majority of the patients were in the 0-50 U/L range i.e. no hepatotoxicity. No patient fell in the 251-500 U/L and > 500 U/L ranges. There was no statistically significance difference between the HIV infected and HIV uninfected cohorts in the ALT1, ALT2 and ALT3 measurements. P = 0.761, 0.367 and 0.197 respectively.

4. DISCUSSION

To our knowledge this is the first analysis of hepatotoxicity using serum alanine aminotransferase ALT in an African HIV and TB treatment program. HIV infection is a risk factor for anti- tuberculosis drug induced hepatotoxicity, so is the use of HAART [18,19]. In our study there was no statistically significant difference between ALT levels between the HIV infected and HIV uninfected group at baseline, 4 weeks, 8 weeks after commencement of antituberculosis drugs.

The low proportion of antituberculosis drug-induced hepatotoxicity (ATDH) in our study is consistent with previous studies in sub-saharan African [20-22]. In a study in Congo DR, TB drug (2HRZE/4HR) were well tolerated among 446 TB patients. They did not report any hepatitis, but increased transaminases levels were occasionally seen [21]. Similarly, in study done in Uganda, only two of 265 HIV infected subjects (1%) developed hepatotoxicity during treatment of pulmonary TB with 2HRZE/6HR [22]. Some workers reported that hepatitis and transaminases elevation did occur during preventive TB treatment in HIV- positive patients and that 0.80% had transaminase levels > 135U/L [23].

All these reports suggest that the incidence of antituberculosis drug-induced hepatotoxicity (ATDH) in adults is low in sub-Saharan Africa. This is unexpected because risk factors such as HIV, hepatitis B and C infection are highly prevalent in this region. The reasons for this low incidence of ATDH are varied. For example, the available studies were not designed to

Table 1. Age, gender and ALT distribution of study population

Variable	PTB only n=205	PTB/HIV co-infection n=251
Age (median and IQR)	32 (17.61)	31(15.65)
Gender (N/%)		
M	57 (27.8)	68 (27.1)
F	148 (72.2)	183 (72.9)
ALT_1 (N/%)		
0 – 50 U/L	171 (83.4)	212 (84.5)
51 – 125 U/L	30 (14.6)	34 (13.5)
126 – 250 U/L	4 (2)	5 (2.0)
Rate of hepatotoxicity	16.6%	15.5%
ALT_2 (N/%)		
0 – 50 U/L	185 (90.2)	229 (91.2)
51 – 125 U/L	18 (8.8)	20 (8.0)
126 – 250 U/L	2 (1.0)	2 (0.8)
Rate of hepatotoxicity	9.8%	8.8%
ALT_3 (N/%)		
0 – 50 U/L	194 (94.6)	235 (93.6)
51 – 125 U/L	11 (5.4)	15 (16.0)
126 – 250 U/L	0 (0.0)	1 (0.4)
Rate of hepatotoxicity	5.4%	16.4%

Table 2. Comparison of ALT levels in patients with PTB only and PTB/HIV co-infection

Variable	PTB only (n= 205)	PTB/HIV co-infection (n= 251)	P value Z-test
Age (years)	33.43±8.10	33.33±9.43	P=0.660
ALT_1 (U/L)	33.02±24.28	33.80±28.82	P=0.761
ALT_2 (U/L)	29.74±18.36	30.21±16.98	P=0.367
ALT_3 (U/L)	26.40±14.39	27.82±15.00	P=0.197

NB: Results are given as Mean ±SD with range in parenthesis

specifically study ATDH, thus, mild or transient hepatotoxicity may have been missed [20].

Furthermore, there is some evidence that absorption of anti-TB drugs in adults with HIV/AIDS is worse compared with non-HIV infected patients [24]. This could explain why ATDH is seen less frequently in our HIV infected population even when HIV infection is a risk factor for ATDH. Some workers have cited the possibility of ethnic variation causing differences in susceptibility to drug toxicity. Phenotypic variation in human drug metabolism can be attributed to polymorphism in genes encoding drug metabolising enzymes. Such polymorphisms may alter enzymes activity and could subsequently increase formation of reactive metabolites [25]. Genetic polymorphism in drug metabolising enzymes may explain the low incidence of ATDH in sub-Saharan populations.

These findings make further studies on ATDH attractive especially if directed specifically at the subject of antituberculosis drug induced liver injury (even when on HAART) and why the incidence is low in our population.

The NGO that was making anti-tuberculosis drugs and HAART available were also responsible for the cost of carrying out ALT estimations at no cost to the patients. A more elaborate liver function would have been much better in a study of this nature. This is the first limitation. Secondly, is the limitation inherent in retrospective studies which means that validated cause of death could not be ascertained.

5. CONCLUSION

The incidence of antituberculosis drug-induced hepatotoxicity is low in our cohort of both HIV infected and uninfected individuals and that this requires further studies to ascertain reason for this unexpected findings.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Kwara A, Flanigan RP, Carter EJ. Highly active antiretroviral therapy (HAART) in adults with tuberculosis: Current status. International Journal of Tuberculosis and Lung Disease. 2005;9:248-254.
2. National tuberculosis, leprosy and buruli ulcer management and control guidelines sixth edition. Federal Ministry of Health, Nigeria. 2014.
3. Yee D, Valiquette C, Pelletier M, et al. Incidence of serious side effects from first line antituberculous drugs among patients treated for active tuberculosis. Am. J. Respir Crit Care Med. 2003;167:1472-7.
4. Burman W. Issues in the management of HIV related tuberculosis. Chin Chert Med. 2005;26:283-294.
5. Verina JK, Nateniyon S, Mankatiriviham W, Sirinak C, et al. HIV care and treatment factors associated with improved survival during TB treatment in Thailand: An observational study. BMG Infect Dis. 2009;9:42.
   DOI: 10.1186/1471-2334-1189-1142
6. Lee WM. Dmg-induced hepatotoxiaty. N Eng J. Med. 2003;349:474-485.
7. Burman WJ, Reves R, Hepatotoxiaty from refampicin plus pyrazinamide: lessons for policy makers and messages for care providers. Am. J. Respir Crit Care Med. 2001;164-1112-1113.
8. Walker U. Antiretroviral therapy induced liver alteration. Curr Opin HIV/AIDS. 2007;2:293-298.
9. Melveron H, Meintjes G, Burman WJ, Maartens G. Complicatioons of antiretroviral therapy in patients with tuberculosis drug interactions, toxicity and immune reconstitution inflammatory syndnome. J. Infect Dis. 2007;196:863-75.
10. Getnet Yimer, Getachew Aderaye, Wondnossen Amogne, Eyasu Makonnen, Eleni Akhillu, et al. Anti-tuberculosis therapy-induced hepatotoxiaty among Ethopian HIV positive and negative patients. PLOS One. 2008;3:e1809.
11. Tostman A, Boerce MJ, Aarnoutse RE, de-Lange WC, Van der Van AJ, et al. Antituberculosis drug induced hepatotoxiaty: Concise up to date review. J. Gastroen-Hepatic. 2008;23:192-202.
12. Khalili H, Dastiti-Khavidaki S, Rasoo/Mejad M, Rezaie L. Antituberculosis drugs related hepatotoxicity, incidence, risk factor, pattern of changes in liver energies and outcome. DARU. 2009;17:163-167.
13. Javadi MR, Shalviri G, Gholami K, Salam Zadeh J, Maghooli G, et al. Adverse reactions of antituberculosis drug in hospitalized patients: Incidence, severtity and risk factor. Pharmaco Epidemol Drug Saf. 2007;16:1104-1110.
14. Shang P, Xiz Y, Liu F, Wong X, Yiian Y, et al. Incidence, clinical features and impact on antituberculosis treatment of anti-tuberculosis drug induced liver injury (ALT) in China. PLOS One. 2011;6:e21836.
   DOI: 21810 213711 journal pone 0621836.
15. Ruhl CE, Ever hart JE. Elevated serum alanine aminotransferase and gamma glutamyl transferase and mortality in the United State population. Gastroenterology. 2009;136:477-485.
16. WHO. Antiretroviral therapy for HIV infection in adults and adolescent: Recommendation for public health approval, Revision; 2006.
   Available:http://www.who.int/en/
17. National Agency for control of AIDS (NACA) National HIV/AIDS. Response Fact Sheet 2011. Update on HIV/AIDS Epidemic and Response in Nigeria; 2012.
   Available:http://w.w.w.naca.gov.ng/
18. WHO. International monitoring of adverse reaction to drugs adverse reaction terminology. Uppsala: WHO Collaborating Centre for International Drug Monitoring; 1992.
19. Yee D, Valiquette C, Pelletier M, Parison I, Rocher I, Menzies D. Incidence of serious side effects from first line ant-tuberculosis drug among patients treated for active tuberculosis. Am J. Resp and Critical Care Medicine. 2003;167:1472-1477.
20. Tostman A, Boeree MJ, Harries AD, Saurageot D, Banda HT, Zijlstra EE. Antituberculosis drug-induced hepatotoxicity is unexpectedly low in HIV-infected pulmonary tuberculosis patients in Malawi. Tropical Medicine and International Health. 2007;12(7):852-855.
21. Perneins JH, St Louis ME, Mukadi YB. Pulmonary tuberculosis in HIV-infected patients in Zaire-A controlled trial of treatment for either 6 or 12 months. N Engl J Med. 1995;332:779–784.

22. Johnson JL, Okwera A, Nsubuga P, Nakibali JG, Whalen CC, Hom D, et al. Efficacy of an unsupervised 8 months rifampicin – containing regimen for the treatment of pulmonary tuberculosis in HIV infected adults. Uganda Case Western Reserve University Research Collaboration. Int J Tuberc Lung Dis. 2000;4(11):1032-40.
23. Whalen CC, Johnson JL, Okwara A. A trial of tree regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Ugandan Case Western Reserve University Research Collaboration. NESM. 1997;337:801-808.
24. Peloquin CA, Nilta AT, Burman WJ. Law antituberculosis drug concentrations in patients with AIDS. The Annuals of Pharmacotherapy. 1996;30:919-925.
25. Wilkinson GR. Drug metabolism and variability among patients in drug response. NEJM. 2005;352:2211-2221.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/10105