ORIGINAL RESEARCH PAPER

Volume-7 | Issue-7 | July-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ANALYSIS OF DRUG INDUCED LIVER INJURY IN HIV PATIENTS ASSOCIATED WITH PROTEASE INHIBITORS- A PROSPECTIVE STUDY AT TERTIARY CARE HOSPITAL

Pharmacology

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ABSTRACT

Background- HIV patients are at increased risk to develop severe hepatotoxicity following initiation of antiretroviral therapy containing HIV-1 protease inhibitors (Pis).

Objectives- To determine risk of hepatotoxicity for HIV seropositive patients on Antiretroviral Protease Inhibitor drugs.

Materials and Methods- The study includes newly diagnosed 280 HIV seropositive patients (aged between 10 and 50 years) who reported to ART centre for treatment at LLRM Medical College & Hospital, Meerut and followed inclusion and exclusion criteria. Epi-info software was used for analysis.

Results- Since after initiation to therapy, serum ALT, AST and ALP levels increased significantly in 60%,62% and 77% patients and the incidence of severe hepatotoxicity within treatment months of Protease Inhibitors was high with Lopinavir/Ritonavir (46%), Indinavir/Ritonavir (45%), Nelfinavir (37%), Saquinavir/Ritonavir (33%) and Indinavir (24%) in HIV patients. Similarly, Hepatotoxicity was significantly higher in HBs Ag and HCV coinfected patients as compared to subjects without coinfection.

Conclusion- Continuous monitoring of ARV administration is required so as to prevent fatal effects of hepatotoxicity.

KEYWORDS

Dili, Protease Inhibitors, Hiv, Hepatitis, Liver Enzymes.

Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus known to be the primary cause of Acquired Immune Deficiency Syndrome (AIDS).More than 33 million people have been diagnosed as infected with HIV (UNAIDS, 2006).Pharmaceutical agents that can be combined to make up highly active antiretroviral therapy (HAART), namely: Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs) and Protease inhibitors (PIs).PI's namely: Nelfinavir, Lopinavir /Ritonavir, Indinavir, Indinavir /Ritonavir, Saquinavir/ Ritonavir.HIV patients are at increased risk to develop severe hepatotoxicity following initiation of antiretroviral therapy containing HIV-1 protease inhibitors (PIs). [1-6] The first sign of damage to the liver is an increase in liver enzyme levels in the blood and can be measured by blood tests. These are called liver function tests (LFTs) include: alanine aminotransferase (ALT) aspartate aminotransferase (AST) Alkaline phosphate (ALP). Liver toxicity is an important complication of HIV infection and in approximately 6% to 30% of treated patients, antiretroviral therapy is associated with significant increases in serum liver enzymes, which may require discontinuation of HIV treatment. [7,8] In addition, because of shared routes of transmission, chronic viral hepatitis is common, with an estimated 30% and 10% of HIV-infected persons co infected with hepatitis virus (HCV) and hepatitis B virus (HBV), respectively. [9-11]. So, the rationale behind the study was to evaluate development of drug induced liver injury associated with antiretroviral drugs that include protease inhibitors in a tertiary care hospital.

Material & Methods

The present study was a prospective cross-sectional analysis conducted over period of 3 years from September 2013 to August 2016 at ART Centre of LLRM Medical college, Meerut. (U.P.). The study was conducted on Newly diagnosed HIV seropositive volunteer patients (in ICTC) who were sent to ART centre for HAART therapy-including protease inhibitors.

Sample Size: Sample size in the present study was calculated on the basis of prevalence of HIV through literature search ie. 0.26% [12] and considering 95% confidence interval, allowable error of 5%. So, the formula used for calculation of sample size (n) was:

$n = z^2pq/d^2$

Where in, z (at 95% confidence levels) = 1.96~2

P (Estimated prevalence of HIV) = 26

q (1 − p) = 74

d (Allowable error) = 5%

Therefore, $n = 2 \times 2 \times 26 \times 74/25 = 308$.

Out of total 308 patients, 11 patients were lost to follow up, 8 patients died during the course of treatment and 9 patients changed the regimen. So, Total 280 patients were studied during the study period.

Methodology

Patients diagnosed and confirmed to be HIV positive at ICTC centre and were sent to ART centre for Antiretroviral therapy. In ART centre all the patients were counselled for the study. Written informed consent forms were distributed and explained to the participants and confidentiality was maintained. The patients who were reconfirmed to be HIV positive underwent liver function test (LFT), hepatitis test and CD4 cell count before initiation of therapy. Group of Protease Inhibitors that were prescribed during study period were Nelfinavir, Lopinavir/ Ritonavir, Indinavir, Indinavir& Ritonavir, Saquinavir & Ritonavir. All the universal precautions were taken while conducting this study.

Data Analysis

The recorded observations were entered in Epi data software and the collected data was consolidated on Microsoft Excel sheets and further analyzed in Epi info 7.1.3.0 version. The results were expressed as proportions and percentages. Chi-square test was used for qualitative variables to find association and P value <0.05 was considered statistically significant.

Results

Table 1- Age and Gender wise distribution of study participants (N=280)

Age (yrs)	Male (%)	Female (%)	Total (%)
10-20	00 (0.00)	05 (12)	05 (2)
21-30	32 (12.76)	27 (68)	59 (21.00)
31-40	144 (60)	8 (20.00)	152 (54.20)
41-50	64 (27.24)	00 (0.00)	64 (22.80)
Total	240(100.00)	40 (100.00)	280(100.00)

Table 2- Administration of Protease Inhibitors in study participants (N=280)

Antiretrovirals	No. of patients	Percentage (%)
PI's exposure		
Nelfinavir	95	36.00
Lopinavir& Ritonavir	40	12.00
Indinavir	47	17.00
Indinavir& Ritonavir	36	13.00
Saquinavir & Ritonavir	62	22.00
Total	280	100.00
NRTI exposure		
Zidovudine	64	35.00
Lamivudine	95	53.00
Tenofovir	22	12.00
Total	181	100.00
NNRTI exposure		
Efavirenz	25	25.00
Nevirapine	74	75.00
Total	99	100

Table 3-Liver Enzymes before and after therapy in study participants

	Before Initiation of therapy		After Initiation of therapy		
	Normal (%)	Raised (%)	Normal (%)	Raised (%)	p- value
ALT	304 (92)	26 (08)	132 (40)	198 (60)	<0.001**
AST	300 (91)	30(09)	124 (38)	206 (62)	<0.001**
ALP	119 (39)	211 (61)	76 (23)	254 (77)	<0.001**

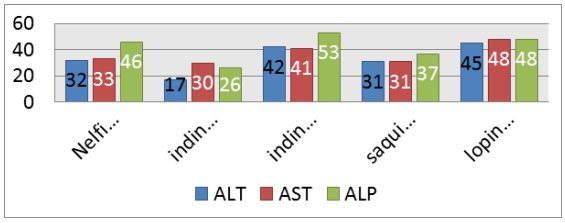

Figure 1- Study Participants with raised enzymes levels

Table 4- Status of Hepatitis B & C in study participants

	Positive (%)	Negative (%)	p-value
HBs Ag	78(28)	202(72)	<0.05*
HCV Antibody	53(19)	227(81)	<0.001**

Table 1 shows out of total 280 HIV positive patients under study, 240 (86%) were males and 40 (14%)were females, the highest prevalence was found in the age group of 31-40 years in males (60%) and 21-30 years in females (68%). This shows that the study was male preponderance.

Table 2 shows out of total 280 patients who were administered Protease inhibitors, most of the patients 95(36%) were administered Nelfinavir, 40(12%) patients were administered Lopinavir and Ritonavir, 47(17%) patients were administered Indinavir, 36 (13%) patients were administered Indinavir and Ritonavir, 62(22%) patients were administered Saquinavir and Ritonavir. Out of total 99 patients who were administered NNRTI, 74(75%) patients were administered Nevirapine. and 25(25%) patients were administered Efavirenz.

Table 3 depicts ALT levels which were normal in 258 (92%) patients and raised in 22(8%) patients before initiation of therapy and were found to be normal in 112 (40%) patients and raised in 168(60%) patients after initiation of therapy. And both before and after initiation of therapy were found to be statistically highly significant. AST levels which were normal in 255(91%) patients and raised in 25(9%)patients before initiation of therapy and were found to be normal in 106(38%)patients and raised in 174(62%) patients after initiation of therapy, and association was highly significant (p<0.001). ALP levels which were normal in 109(39%)patients and raised in 171(61%)patients before initiation of therapy and were found to be normal in 64(23%)patients and raised in 216(77%)patients after initiation of therapy and was found to be statistically significant both the times.

Figure 1 shows on comparison of Liver enzymes before and after initiation of Protease Inhibitors, it was seen there was significant increase in liver enzymes levels after initiation of therapy as compared to before. The significance level was seen in all liver enzymes i.e ALT, AST, ALP with protease inhibitors but the toxicity level was seen highest with Lopinavir/Ritonavir (46%), Indinavir/Ritonavir (45%), Nelfinavir (37%), Saquinavir/Ritonavir (33%) and Indinavir (24%).

Table 4 concludes that before initiation of therapy, 78(28%) patients were HBsAg positive and 202(72%) patients were HBsAg negative and it was found to be statistically significant association. In case of HCV Antibody before the initiation of therapy 53(19%) were positive and it was found to be highly significant association and 227(81%) patients were HCV antibody negative.

Discussion

A study conducted by Miller et al. [13], on 19 patients, shows a significant increase in liver enzyme due to antiretroviral drugs combination of anti-retroviral therapies such as – Triple – Nuc, NRTI+ NNRTI or NRTI +PI. Similar results were seen in other studies [8,9,10]. In 2013, A study was conducted by Ranjit Patil et al.[14] on 179 patients, In this study ,mean ±SD serum ALP and GGT in control group was found to be 43.12 ± 4.13 IU/L & 19.52 ± 2.93 IU/L which was increased to 129.5±126.12 IU/L (p<0.001) [Max range = 782 IU/L] & 57.27 ± 26.35 IU/L (p<0.01)[max range =154 IU/L] in HIV positive patients. The increase was significantly significant (P<0.01).

Conclusion

The incidence of severe hepatotoxicity within treatment months of Protease Inhibitors was high with Lopinavir/Ritonavir (46%), Indinavir/Ritonavir (45%), Nelfinavir (37%), Saquinavir/Ritonavir (33%) and Indinavir (24%) in the present study. Frequent monitoring of Liver enzymes (AST, ALT and ALP) in the first three months is necessary in all patients initiating HAART- including Protease inhibitors and concurrent Hepatitis treatment to avoid missing hepatotoxicity which is not included in routine tests.

Conflict of Interest- None declared

Source of Funding- Nil

Acknowledgement- The authors like to thank all the participants who have given consent and without there support this study was not possible. We also like to thank Dr.Shubhanshu Gupta (Assistant Professor, Dept of Community Medicine, GMC, Datia) for his unconditional help and support in statistics and research methodology.

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