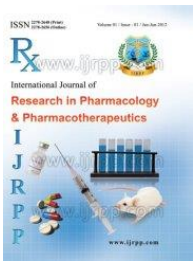
International Journal of Research in Pharmacology & Pharmacotherapeutics



ISSN Print: 2278-2648 ***IJRPP |Vol.7 | Issue 1 | Jan - Mar - 2018***
ISSN Online: 2278-2656 ***Journal Home page: www.ijrpp.com***

Research article ***Open Access***

Hyperbilirubinemia during Atazanavir treatment in HIV/AIDS patients taking second line ART drugs

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ABSTRACT

Background

Hyperbilirubinemia is frequently observed in HIV (Human Immunodeficiency Virus) patients treated with Atazanavir containing antiretroviral regimen in the dose of 300 mg once daily. However, little is known about the incidence of Atazanavir-associated hyperbilirubinemia in Asian population. Hyperbilirubinemia is defined as an excess of bilirubin in blood either conjugated or unconjugated.

Aim

To estimate the incidence of Atazanavir associated hyperbilirubinemia in HIV patients receiving second line antiretroviral regimen advocated by National AIDS Control Organisation (NACO) by measuring serum bilirubin levels.

Materials and Methods

The study was done in 100 HIV-infected patients attending ART Plus centre at a tertiary care centre receiving Atazanavir regimen for a period of 12 months. The bilirubin levels in blood were estimated by MALOY & EVELYN METHOD.

Results

The incidence of grade I hyperbilirubinemia was 26%, grade II was 24%, grade III was 48% & grade IV 2%. The Study data suggested that Atazanavir-associated hyperbilirubinemia is common and self limiting.

Conclusion

It was observed that most of the HIV/AIDS patients receiving Atazanavir containing ART regimens developed hyperbilirubinemia, so these patients should be regularly monitored for Atazanavir induced hyperbilirubinemia.

Keywords: HIV, Acquired Immunodeficiency Syndrome, Atazanavir, Hyperbilirubinemia, NACO.

INTRODUCTION

HIV is a retrovirus which belongs to family retroviridae, subfamily lentiviridae that causes chronic persistent infection with gradual onset of symptoms leading to immune-suppression, making the patient more vulnerable to opportunistic infections and finally death. At the end of 2016, an estimated 36.7 million people [34.0 million–39.8 million] were living with HIV worldwide. Globally there were 1.8million new HIV infections and 1.1 million people died of AIDS-related causes in 2016. [1] HIV/AIDS is the world's sixth largest cause of death in humans, accounting 3.1% of all deaths. [2] India ranks third among the countries having most number of HIV-infected people and HIV related deaths in the world. [3]

Treatment of HIV with monotherapy has been associated with high mutation rates and has been discontinued. [4] The two options for initial therapy most commonly in use today are two different regimens with three drugs in each regimen. The first line regimen consists of two nucleoside analogues (Zidovudine/Stavudine and Lamivudine) and a non-nucleoside reverse transcriptase inhibitor (Nevirapine/Efavirenz). The second line consists of two nucleoside analogues and a protease inhibitor. [5] Second line ART drugs are initiated in those patients who are showing immunological failure to first line drugs and those who are not tolerating first line regimen. The common second line regimen advocated in this set up includes Tenofovir + Lamivudine + Ritonavir boosted Atazanavir. [6]

Atazanavir is an azapeptide protease inhibitor with a pharmacokinetic profile that allows once-daily dosing, low pill burden, and has fewer effects on patient's lipid profile compared with other protease inhibitors. [7] Currently approved Atazanavir doses in HIV infected patients are two 200mg capsules with ritonavir [boosted] once daily. The most common side effects encountered with Atazanavir are nausea, vomiting, diarrhoea, abdominal pain, headache, peripheral neuropathy, skin rash, fat mal-distribution, hyperglycaemia, PR interval prolongation on ECG and indirect hyperbilirubinemia (7-8%). [8] Atazanavir-associated hyperbilirubinemia is defined as hyperbilirubinemia developing after initiation of Atazanavir therapy in the absence of other causes of hyperbilirubinemia.

According to WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection 2016, indirect hyperbilirubinemia (clinical jaundice) is a major type of toxicity associated with ritonavir boosted Atazanavir (ATV/r) therapy. But this phenomenon is clinically benign but potentially stigmatizing. WHO consolidated guidelines 2016, mentioned to substitute only if adherence is compromised. [9]

The occurrence of hyperbilirubinemia with Atazanavir is relatively frequent, generally reversible and often a rare cause of treatment discontinuation (<1%) where the bilirubin was predominantly of unconjugated type. [10] Normally unconjugated bilirubin gets conjugated with glucuronic acid and is excreted in the bile with the help of microsomal enzyme UDP-glucuronosyltransferase (UGT). [11] Atazanavir competitively inhibits UGT1A1 enzyme alleles and elevates bilirubin levels. [12, 13]

Second line ARVs has been recently introduced in National AIDS Control Programme of India and its effectiveness and adverse effect profile is not widely studied in Indian patients. The main aim of conducting this study was to assess the hyperbilirubinemia during Atazanavir treatment and its impact on quality of life of the patient.

MATERIALS AND METHODS

Study design

This was a longitudinal observational study. The study protocol was approved by institutional ethical committee. A written informed consent was taken from all patients who were included in the study in their local language. The study was done at ART Plus centre, at a tertiary care hospital. A total of 100 patients were included in the study. All the HIV-infected patients who were initiated with second line antiretroviral regimen containing Atazanavir (300 mg per day) were studied. Total bilirubin levels and liver functions tests were noted at the time of initiation of 2^{nd} line therapy consisting of Tenofovir + Lamivudine + Atazanavir + Ritonavir and at the end of 6 and 12 months of treatment. Antiretroviral regimen was managed by the board certified infectious disease specialist i.e NACO.

The patients receiving first-line ARV drugs from National AIDS Control Organisation (NACO) for at least six months and suspected of having treatment failure were examined by State AIDS Clinical Expert Panel (SACEP). These patients were evaluated clinically, immunologically (CD4 count) and

virologically (plasma viral load). Patients in the age group of 18-70 years who were started on 2nd line ART therapy after failure of 1st line therapy as per NACO guidelines were included and patients who were pregnant, lactating, having pre-existing abnormal liver, renal function tests, lipid profiles were excluded.

Grades of hyperbilirubinemia

Hyperbilirubinemia was graded from grade 1 to grade 4 in accordance with the AIDS Clinical Trials Group guidelines for total bilirubin levels: grade 1(1.3-1.9 mg/dl); grade 2(1.9-3.1 mg/dl); grade 3(3.1-6.1 mg/dl); and grade 4(>6.1 mg/dl).

STATISTICAL ANALYSIS

Data was collected using a data extraction sheet and data was processed and analyzed using Microsoft excel 2013 and statistical package for social sciences (SPSS) for windows version 21 and the analysed data was expressed in percentages [*n* (%)]. 't' test and Chi square test were applied. P value < 0.05 was considered significant (0.01).

RESULTS

Age and gender wise distribution

One hundred patients were enrolled into the study. Out of 100 patients, 5.26% (n=5) belonged to 15 – 25 years, 25.2% (n=24) belonged to 26 – 35 years, 43.1% (n=47) belonged to 36 – 45 years, 18.9% (n=18) belonged to 46 – 55 years and 1.05% (n=1) patients belonged to age group 55 – 65 years. Maximum number of patients i.e 43.1% (n=47) and 25.2% (n=24) belonged to age groups 36 – 45 years and 26 – 35 years. The median age for patients being 39 years.

In the first 6 months of treatment, 5 patients died on second line ART. After 12 months there were no deaths or lost to follow ups. So 95cases on second line ART were available for evaluation. There were zero dropouts and 5% deaths at the end of treatment.

Out of 100 patients, 71 were males and 24 were females. It was found that 52.6% (n=50) of HIV patients who were on Atazanavir regimen showed hyperbilirubinemia. Out of 50 patients, 56.3% (n=40) were males, and 41.6% (n=10) were females and had hyperbilirubinemia according to table no.1.

Table no.1: Sex wise distribution

S.No	Sexwise distribution	Without Hyper-bilirubinemia	With Hyper-bilirubinemia	Total
1.	Male	31 (43.6%)	40 (56.3%)	71
2.	Female	14 (58.3%)	10 (41.6%)	24
3.	Total	45 (47.3%)	50 (52.6%)	95

Incidence of hyperbilirubinemia was measured. 55.0% (n=22) of males and 20.0% (n=10) of females had grade III hyperbilirubinemia. (Table no.2)

Table no.2: Sex wise distribution of grades of hyperbilirubinemia

S.no	Sex	Grade I	Grade II	Grade III	Grade IV	Total
1.	Male	9 (22.5%)	8 (20.0%)	22 (55.0%)	1 (2.5%)	40
2.	Female	4 (40.0%)	4 (40.0)	2 (20.0%)	0 (0%)	10
3.	Total	13(26.0%)	12 (24.0)	24 (48.0%)	1 (2%)	50

As per table no.3.Hyperbilirubinemia was more in the age group of 36-45 years accounting for 48.0% (n=24).

Table no.3: Age wise distribution

S. no	Age in years	Patients with hyperbilirubinemia	Percentage %
1.	15-25	3	6.0%
2.	26-35	11	22.0%
3.	36-45	24	48.0%
4.	46-55	11	22.0%
5.	56-65	1	2.0%
	Total	50	100%

Hyperbilirubinemia was graded from grade 1 to grade 4 in accordance with the AIDS Clinical Trials Group guidelines for total bilirubin levels: grade I (1.3-1.9 mg/dl); grade II (1.9-3.1 mg/dl); grade III (3.1-6.1 mg/dl); and grade IV (>6.1 mg/dl). In this study it was identified that incidence of hyperbilirubinemia was more of grade 3(48%). The incidence of hyperbilirubinemia as per different grades was shown in figure no:1.

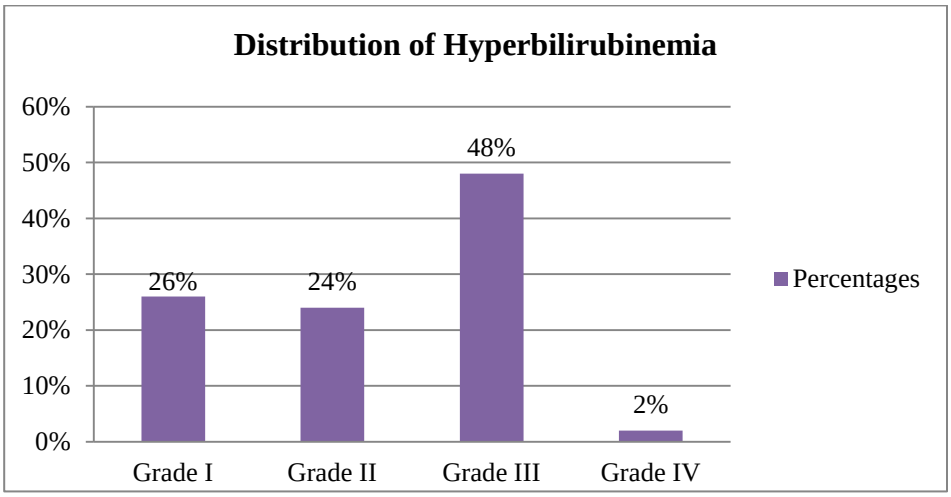

Fig no.1: Grades of Hyperbilirubinemia.

It was observed that mean levels of CD4 after six months of therapy were elevated compared to the baseline values. There was a significant increase in mean CD4 count at 6 months (180.37/cu.mm) and 12 months (266.04/cu.mm) as compared to baseline (66.35/cu.mm) ($P < 0.0001$). However, an increase in mean CD4 count was significantly more at 12 months in patients treated with second line ART regimen [266.04 cells/mm] ($P < 0.05$). The increase in CD4 count and decrease in plasma viral load were extremely statistically significant ($P < 0.0001$). (Table no.4)

Table no.4: Assessment of weight, CD4, PVL & Hb

Parameters	Mean ± SD			't' test	'P' Value
	Baseline	6 months	12 months		
CD4 Count	66.35±40.55	180.37±45.05	266.04±74.07	23.647	0.0001
Plasma Viral Load	212068.40± 55641.41	----	164840.24± 86680.24	4.585	0.0001

At the end of 12 months of treatment 51 patients showed an increased serum bilirubin levels with an elevated liver function tests. There was an increase in mean serum bilirubin (1.14 mg/dl) and SGOT and SGPT (39.0 IU/dl & 37.48 IU/dl) from baseline values (0.76mg/dl, 34.47 IU/dl, 28.53 IU/dl).

Table no.5: Hepatic ADRs

Parameters	Mean ± SD			't' test	'P' Value
	Baseline	6 months	12 months		
SGOT	34.47±13.37	42.01±10.61	39.0±8.14	2.820	0.0053
SGPT	28.53±10.12	37.75±7.20	37.48±7.92	6.788	0.0001
Bilirubin	0.752±0.21	1.27±0.26	1.14±0.23	12.34	0.0001

DISCUSSION

Despite the success of HAART, AIDS-related issues/problems still persist and some new challenges with respect to HIV, ARV drugs and HIV infected patients have emerged. HIV infection is now recognized as chronic persistent infection. There are increasing reports of multi-drug resistant (MDR) virus in treatment experienced patients. All these patients require new regimen for continual viral suppression. The problem of drug resistance has led to the concept of second line anti retroviral therapy (ART).

In the present study we have observed a total of 100 HIV positive patients receiving antiretroviral regimen containing Atazanavir in the dose of 300 mg once daily for the incidence of hyperbilirubinemia. Out of 100 patient's majority i.e n=71 were male and amongst these 40 of them had hyperbilirubinemia. The mean age of patients in this study was 39years as compared to the median age of 41years in Choe PG, et al,. study [14] and this is also comparable to a study done by subashini et al [15] where majority are males (78.38%), with the median age of 36 years (IQR: 30.5–41.5).

Majority of patients with HIV who has shown immunologic failure to first line therapy achieved viral suppression after switching to second line therapy. This has been demonstrated in the present study by substantial mean increase in CD4 count in patients on second line therapy, an average of 180 cells/cu.mm over 6 months period. This is comparable to a median CD4 count increase at 12 months of 135 cells/cu.mm by Pujades Rodriguez M et al. [16] In comparison the average gain of 114 cells in 6 months on second line seen in our study represents substantial immune recovery. With second line regimen there was a significant increase in CD4 count at 6 and 12 months 83% (n=79) and 86% (n=82).This was also observed in study at Kolkata, India (Guha SK et al.,2011). [17]

Out of 95 patients, 52.6% (n=50) developed hyperbilirubinemia which was comparable to 44% in Castle study [18] and 67% in Rotger M et al study. [19] Hyperbilirubinemia was more in the age group of 36-45 years accounting for 48.0% (n=24). In the present study grade I (26%) and III (48%) hyperbilirubinemia was more common where as in Castle study [18] and Choe PG, et al., study, [14] grade III and IV were more common. Robert L Murphy et al [20] reported the abnormal LFT's in 3% and 5% of cases, while in the present study the increase in SGOT and SGPT were 40% and 42% with Atazanavir regimen.

The above studies were done in Korean and American population and the present study was done in Indian population. So, the difference in incidence of hyperbilirubinemia may be due to genetic variation because of racial and ethnic differences.

CONCLUSION

In conclusion, it was observed that most of the HIV positive patients receiving Atazanavir in ART regimen were found to develop transient hyperbilirubinaemia. So, these patients should be regularly investigated and followed up for bilirubin levels and counselled accordingly to avoid discontinuation of the regimen due to cosmetic concerns like sclera icterus and jaundice.

Limitations of the study

1. More number of study groups are needed to confirm the observation.
2. The major limitation of this study was lack of facilities for observing gene polymorphisms responsible for this condition.
3. Factors other than Atazanavir could have affected bilirubin metabolism. To minimize the effect of possible confounders we excluded patients with active liver disease.
4. Unable to exclude the effect of other two drugs on bilirubin metabolism.
5. The patients were followed for a limited period of 12 months though the patients received these drugs for lifelong.

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