Highly Active Anti-retroviral Therapy Associated Hepatotoxicity: Case Report and Discussion

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ABSTRACT

Anti-retroviral Drugs (ARV) drugs are always given in combination of two or three drugs like Tenofovir, Lamivudine, Efavirenz and is often referred as HAART therapy. Though it has potential to reduce the disease progression, it is often associated with adverse drug reactions like hepatotoxicity which has been the concern till date. We present here a case of 42-year-old patient who developed hepatotoxicity induced by ARV drugs with apparent risk factors of female gender and higher CD_4 count. This case stresses the need for careful evaluation, regular monitoring and prompt omission of drug on suspicion of hepatotoxicity in reducing the mortality and morbidity in HIV infected patients.

Key words: Antiretroviral - therapy, Hepatotoxicity, Adverse drug reaction, HIV, HAART.

INTRODUCTION

The mortality of HIV (Human Immunodeficiency Virus) and its opportunistic infections has greatly decreased with the extensive use of Highly Affective Anti-Retroviral Therapy (HAART) which employs a combination of two or more anti-retro viral drugs that includes nucleoside, non-nucleosidereverse transcriptase inhibitors and protease enzyme inhibitors.[1] Although HAART has the potential to reduce the mortality of HIV and its opportunistic infections, it is always associated with adverse effects by which the patients may present with AIDS related illnesses.[2] One of the common Adverse Drug Reaction (ADR) associated with HAART is hepatotoxicity and the others include hematuria, Gastro intestinal disorders, bone disorders etc.[3] There are several mechanisms of developing hepatotoxicity due to ART drugs and it has become the primary cause of death in HIV infected patients rather than AIDS related illnesses.[4] It is important that before initiating the HAART the physicians should be more cautious and concern about the ADRs of HAART.

CASE REPORT

A 42-year-old female patient was diagnosed as HIV positive six months back and was on Highly Active Anti retroviral therapy (HAART). Her HIV viral load was 35,71,428 copies/ml with absolute CD_4 count of 570 cells/mm^3. She started using HAART comprising Tenofovir (TDF), Lamivudine (3TC) and Efavirenz (RTV), without any concomitant medications. Her liver function tests were then normal. 3 months after initiation of therapy she developed fever which was intermittent, moderate grade and increasing in evening. After one month she developed with icterus associated with vomiting and loss of appetite with which she was hospitalised. On examination icterus and mild dehydration were only the positive findings. Investigations showed a surge in liver enzymes and serum bilirubin (conjugated and unconjugated). Markers for viral hepatitis were negative and stool examination was normal (Table 1). Abdominal ultrasound showed the evidence of hepatomegaly, fatty infiltration and moderate ascites. The haemoglobin was decreased and on hemogramit showed that she had normocytic normochromic

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Table 1: Showing the laboratory data of patient after admission in to hospital and after initiation of treatment.

Tests	Units	Reference range	On admission	After treatment
AST(SGOT)	IU/L	5.0-40.0	190	55
ALT(SGPT)	IU/L	5.0-40.0	146	57
ALP	IU/L	44-147	410	150
Total Bilirubin	Mg/dl	0.2-1.3	9.8	1.9
Direct Bilirubin	Mg/dl	0.1-0.8	3.3	1.5
Serum Albumin	g/dl	3.5-5.0	3.5	3.6
Serum Globulin	g/dl	2.0-3.5	2.7	2.8
Total protein	g/dl	6.0-8.0	6.2	6.3

anaemia with leukocytosis. The treatment given was that HAART was withheld and intravenous antibiotics and hepatoprotectives were administered and she was given packed cell transfusion to have her anaemia get corrected. After treatment with antibiotic ceftriaxone, antipyretics and hepatoprotectives and supportive therapy for 9 days, the patient's complaints were subsided and her liver enzymes and serum bilirubin were optimal. The patient was discharged and advised to continue ART.

DISCUSSION

Initiation of HAART (TLE or ZLN) to HIV infected patients is most often challenging to prescribers as it is often associated with serious adverse events like hepatotoxicity, hematuria, decreased bone density, cardiovascular diseases and gastrointestinal infections. Among these, HAART induced liver injury is one of the major side effect[3] and appears as a major cause of death according to a recent report.[4] The increase in incidence of hepatotoxicity due to the TLE therapy has been the concern till date.

The risk factors for developing hepatotoxicity in patients receiving TLE therapy are female gender, chronic hepatitis virus (hepatitis B or hepatitis C) co-infection, higher CD_4 cell counts (especially women with CD_4 cell counts $\geq$ 250 cells/mm^3) and abnormal base line levels of serum transaminase enzyme.[5]

The highest risk period for developing liver injury is initial 4 weeks of therapy and is characterised by symptomatic events like malaise, fatigue, nausea, abdominal discomfort and jaundice and elevated serum transaminase levels.[6]

In our patient, the possible cause of hepatotoxicity is antiviral drug toxicity and acute viral hepatitis due to hepatitis virus (hepatitis B or hepatitis C).[7] As the patient is presented with negative laboratory reports of hepatitis B or C infection and with a CD_4 count of 570 cells/mm^3, TLE therapy is more likely to cause liver injury.

TLE regimen is the combination of Tenofovir (protease inhibitor), Lamivudine (nucleoside reverse transcriptase inhibitor) and Efavirenz (non-nucleoside reverse transcriptase inhibitor). Among the drugs of TLE therapy, non-nucleoside inhibitors (NNRTI's), compared to nucleoside reverse transcriptase inhibitors (NRTI's) are more likely to cause hepatotoxicity.

There are several mechanisms explaining the liver injury which results as a consequence of metabolism and/or due to direct cell toxicity by NNRTI's. The mechanisms by which ARV drugs induced toxicity arises includes direct cholestatic injury (bile acid retention and apoptosis), mitochondrial dysfunction, Endoplasmic Reticulum (ER) stress and hepatocytes membrane damage by reactive oxygen species.[8]

In any of the above mechanism, liver biomarkers like transaminases, alkaline phosphatase and other liver function tests including conjugated and unconjugated bilirubin becomes elevated and serum protein levels gets decreased. These findings in this patient were clinically evident of TLE therapy induced liver injury.

If, after thorough clinical assessment, hepatotoxicity is confirmed in patients undergoing HAART therapy and one or more antiretroviral drugs is believed to be a causative factor, the only effective treatment till now is discontinuation of the causative agent.[9] The treatment should be discontinued for a short period so that the liver can recover from injury as it has a natural regenerating capacity. Though the liver can regenerate, its recovery depends on the dosage and the severity of the toxicity. In this case, it may be advantageous to completely stop all antiretroviral therapy rather than just one or two agents. This was done to minimise the potential for development of individual drug resistant strains. Frequent assessment of disease progression (CD_4 count) in the patient is necessary after discontinuation of therapy.

CONCLUSION

Lifelong anti retroviral therapy is necessary to prevent disease recurrence and/ or exacerbation in HIV infected individuals and is effective in prolonging survival. However, it is limited by significant tolerability issues, including hepatotoxicity. To overcome the above challenge, frequent monitoring of patients for the levels

of HAART toxicity is necessary especially in early phases of treatment. Thus, a physician should be vigilant to adverse drug reactions to HAART and have to establish a balance between efficacy and toxicity in design of drug regimen.

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CONFLICT OF INTEREST

No conflicts of interest.

ABBREVIATIONS

HIV: Human Immunodeficiency Virus; **HAART:** Highly Active Anti-retroviral Therapy; **ARV:** Anti-Retroviral; **AIDS:** Acquired Immunodeficiency Syndrome; **ADR:** Adverse Drug Reaction; **TLE:** Tenofovir Lamivudine Efavirenz; **ZLN:** Zidovudine Lamivudine Nevirapine; **NRTI:** Nucleoside Reverse Transcriptase Inhibitor; **NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitor; **ER:** Endoplasmic Reticulum.

SUMMARY

HAART is a combination therapy of anti retroviral drugs which is being used extensively to reduce the mortality of patients due to HIV and its opportunistic infections. HAART is often associated with adverse drug reactions like hepatotoxicity, hematuria, gastrointestinal disorders, bone disorders etc. Hepatotoxicity is one of the serious ADR of concern as it has become the primary cause of death in HIV infected patients rather than AIDS related illnesses. Herein a case of adult female is described who developed hepatotoxicity after 6 months of anti-retroviral therapy. This case emphasized the need for regular monitoring of liver enzymes, prompt omission of drug upon suspicion and care evaluation of therapy in reducing the morbidity and mortality of the patient.

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