CASE REPORTS

Dolutegravir induced sub-acute hepatic failure in HIV positive treatment naïve man in Botswana

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ABSTRACT

Dolutegravir associated hepatic failure has rarely been reported. Hepatic failure can occur either acutely or after few weeks as it happened in our patient. We report a case of 61 years old HIV-positive treatment naïve patient who started experiencing features of hepatic injury one month after starting Dolutegravir-based regimen. Patient presented late with overt hepatic failure. We emphasize the importance of close monitoring both at initiation and long-term so as identify patients with early hepatic injury and limit fatal outcomes which are potentially avoidable.

Key Words: Antiretroviral therapy, Dolutegravir, Hepatotoxicity, Human Immunodeficiency Virus

1. INTRODUCTION

Dolutegravir (DTG) was introduced in Botswana at the beginning of year 2016 in the "treat all campaign" as one of the medications in the combination antiretroviral therapy (ARV).[1,2] It belongs to the second-generation integrase inhibitors group and it has been shown in randomized control trials (RCTs) to be non-inferior to other ARVs.[3–5] in terms of potency and safety profile with only about 2% of patients being discontinued on DTG due to adverse effects.[4–8]

Despite the safety profile depicted for DTG in RCTs; there have been raising concerns in real life situations; this is especially true as regards to reported episodes of neuropsychiatric adverse effects which have led to discontinuations[9,10] Hepatotoxicity is a rare recognized complication of DTG which can present as raised transaminases or liver failure; occurring in less than 1% of patients in RCTs. The Botswana HIV treatment guidelines recommend that monitoring of hepatotoxicity to DTG be done especially in patients with underlying liver disease such as chronic Hepatitis B or C.[2]

2. CASE PRESENTATION

We report a case of a 61-year-old male who was asymptomatic 8 months ago; diagnosed to be HIV positive on routine testing and started on highly active antiretroviral (HAART) (Tenofovir/ Emtricitabine/ Dolutegravir) as per National Guidelines.[2] At the time of HAART initiation, his liver enzymes (AST and ALT) and functions (bilirubin) were recorded within the normal reference laboratory ranges. Patient started to experience right upper quadrant abdominal pain after one month of HAART initiation. He described the pain to be intermittent and of dull character, non-radiating, with no obvious relieving or aggravating factors. The abdominal pain was followed by yellowing of eyes few weeks later. Despite this illness and patient attending clinics for medications refill, he only sought medical attention 5 months after starting HAART. At this point, he had noticed abdominal

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distension that was progressively worsening. He reported to get tired easily even after minimal exertion. There was no history of orthopnea or paroxysmal nocturnal dyspnoea.There was associated weight loss exemplified by loose clothing and he also admitted to have poor appetite. There was history of nausea and intermittent vomiting, which contained food materials with occasional mix with speaks of blood. There was associated history of swelling of both lower limbs. Patient also reported to have persistent sleep disturbances; he would fall asleep during the day but stay awake most of the night. He admitted to having several episodes of memory loss & and feeling confused. There was no history of passing dark urine or pale stools; he also denied history of itching. He denied history of fevers or drenching night sweats. He denied history of recent travel, exposure to pesticides, use of intravenous drugs or use of acetaminophen. He had never consumed alcohol or smoked cigarrates and was not sexually active for over the past five (5) years. He was not known to have liver disease. Patient had negative history of any other chronic conditions such as Diabetes mellitus or Hypertension and he was not on any other medications apart from HAART. Serological screening for Hepatitis B surface antigen (HBsAg) and Hepatitis C Virus antibodies prior to admission were negative. Serology for Hepatitis A and E were not performed. Autoimmune screening with antinuclear antibody (ANA) and Anti-smooth antibodies (ASMA) were negative. Physical examination of the patient at the time of admission revealed an elderly chronically ill looking man who was not in cardiopulmonary distress., Hhe had temporal wasting; he was pale and also had sclera icterus. He was not dehydrated, no flapping tremors or gynaecomastia; however he had bilateral pitting lower limb oedema to the level of the ankles. His vitals were; - Pulse rate = 89 beats/min, Blood pressure = 82/63 mmHg, Respiratory rate = 16 breaths/min and Temperature = 35.70°C . Abdomen examination revealed moderate distention without obvious distended veins; tender right upper quadrant, positive shifting dullness and fluid thrill with difficulties to assess for hepatosplenomegaly. Bowel sounds were audible and normal. The rest of systematic examinations including respiratory, cardiovascular and central nervous systems were unremarkable. At the time of admission, investigations revealed normal electrolytes; serum creatinine and urea done 6 weeks prior to admission were 66 μmol/L and 3.25 μmol/L respectively. Patients International Normalized Ratio (INR) done two (2) weeks prior to admission was elevated at 2.93. Results of liver enzymes prior to admission could not be traced. The HIV disease was well controlled with CD4 of 368 cells/μl and undetectable viral load. On the day of admission; Full blood picture revealed normal leukocytes and differentials with mild normocytic anemia (Haemoglobin of 10.1 g/dl). Patient had thrombocytopenia with platelet of 88×10^9/L. The liver enzymes and functions were markedly elevated as follows; Alanine Transaminase (ALT) = 425 U/L (11-41), Aspartate Transaminase (AST) = 595 U/L (10-34), Alkaline Phosphatase (ALP) = 212 U/L (35-110), Gamma Glutamines (GGT) = 75 U/L (11-50), Direct bilirubin = 156 μmol/L (0-3), Total bilirubin = 271.2 μmol/L (1-25.7), Albumin = 15 g/L (35-55), INR = 3.57. Serology for anti-mitochondria antibodies was negative. Abdominal pelvic ultrasound revealed massive ascites, hepatomegaly of 14 cm, with multiple hypoechoic lesions without focal hepatic lesions, there was no splenomegaly and kidneys were of normal size without loss of corticomedullary differentiation. Ascitic fluid biochemistry revealed protein level of 9.4g/L (< 30) consistencye with a transudate. Patient was diagnosed to have sub-acute hepatic failure most likely due to an adverse drug reaction; Dolutegravir was the most likely agent as Tenofovir and Emtricitabine are not associated with hepatic injury[11] and patient was not on either any other pharmacotherapy or traditional medicines. Patient score according to Naranjo scale was 5[12] categorized as "probable" adverse drug reaction. He was categorized as having Grade 2 hepatic encephalopathy; as well Child-Pugh Turcotte Class "C". He had multiple episodes of hypoglycemia which were managed per protocol. He was put on oral metronidazole, lactulose and maintenance intravenous fluids. Liver biopsy was deferred as INR continued to rise (INR was 4.69 on day 7 of admission). Liver transplant services are not available in our setting; patient demised on day 9 of admission with relatives not consenting for autopsy.

3. DISCUSSION

Sub-acute hepatic failure is defined as hepatic failure that presents with either jaundice or encephalopathy from within 29 days to 12 weeks of exposure to causative factors; with most common causes being non-viral hepatitis (A, B, C). Drugs are the ones mostly associated with sub-acute hepatic failure, this is in contrast to hyperacute hepatic failure that occurs within 7 days and is usually related to Hepatitis viruses (A, B, E).[13] Despite the fact that we did not perform serology for Hepatitis A and E; we believe that these etiologies are unlikely given the delayed onset of symptoms.

Drug-induced liver injury (DILI) is a clinical-pathological diagnosis with presentations ranging from raised liver enzymes to acute liver failure. It is known to occur in up to 18% of patients started on ARVs.[14] Risk factors for DILI include underlying liver disease such as chronic hepatitis B and C, age, gender and host genetic factors.[15–18]

DTG as a component of combination therapy for HIV infection has been shown in several clinical trials to have low

propensity for serious adverse events, accounting for only about 1%; these being mostly hypersensitivity reaction in the form of skin rash and liver dysfunction.[4,6,19,20]

Evidence from previous studies revealed that neuropsychiatric manifestations such as sleep disturbances and irritability were a main reason to discontinue DTG;[21] with age more than 60 years and female gender implicated in most adverse events.[22,23]

Liver biopsy is always used to establish pattern of liver injury and underlying chronic liver disease in DILI; however it should be noted that there is no hallmark pattern for DILI. Hence diagnosis of DILI relies on temporal association between a causative drug and onset of liver injury as it happened in our index patient; the latency of association ranges from few days to several months.[24] Exclusion of other possible causes of liver injury from history, serology and radiological investigations is paramount to establish diagnosis of DILI. Despite the fact that prompt withdrawal of offending agent is recommended; patient who are in acute or sub-acute hepatic failure stage needs liver transplantation as a lifesaving management.[24]

Our case report is interesting as it highlights a fatal outcome that could have been avoided. Patient education to understand and report side effects of DTG as well as monitoring of liver enzymes in the early weeks to months after HAART initiation might have altered the course of our patient. Our case report is the first one to be reported in resource limited setting outside RCTs. It is noteworthy that DTG is still a new drug with most RCTs done in developed countries. We have observed only two cases of DTG hepatic failure in English literature.[11,25] There is a high need to conduct studies on adverse events of DTG in the local setting so as to establish patients at risk and subsequently use information to guide clinical practice and limit potential fatal outcomes.

4. Conclusion

We have reported a case of a patient who presented late after few months of symptoms of liver dysfunction; with only Dolutegravir being the possible implicating agent. It is imperative that medical personal be trained to identify early side effects of DTG that warrant discontinuation. Patients should also be given education on adverse effects and report as soon as they notice such symptoms. We recommend studies in resource limited settings on DTG adverse events to foster understanding on burden of adverse events and predisposing factors.

Conflicts of Interest Disclosure

The author declares no conflict of interest

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