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Case Report

Immunological Clearance Following Treatment of Chronic Hepatitis B with Nucleotide Analogue-A Case Report

Uchenna C. Okonkwo.[1], Mbang Kooffreh-Ada.[2], Evaristus Chukwudike.[3], Ogbu E Ngim.[4]

[1]Senior lecturer/Consultant, Gastroenterology/Hepatology University of Calabar Unit, Cross River State, Nigeria.
[2]Lecturer/Consultant, Gastroenterology/Hepatology University of Calabar Unit, Cross River State, Nigeria.
[3]Senior registrar, Department of Internal Medicine, University of Calabar, Cross River State, Nigeria.
[4]Professor/Consultant, Department of Surgery, University of Calabar/JIL Specialist Hospital, Calabar. Cross River State, Nigeria.

*Corresponding Author
Uchenna C. Okonkwo

Abstract: **Background-** Infection with hepatitis B virus (HBV) remains an important global public health problem with significant morbidity and mortality. Nucleotide analogues with high barrier to resistance are thought to be very effective in inducing long-term viral suppression but rarely HBsAg loss. **Case report**- we report the case of a 56year old lady, who presented with a positive HBsAg result detected following a febrile illness. No jaundice or other symptoms referable to a liver disease. She was hypertensive and diabetic with good control. HBV DNA was 2099IU/L, HBeAg was negative, ALT was 10IU/L, Creatinine was 0.76mg/dl. Haematocrit and platelets were within normal limits. Ultrasound showed generalized increased echo-pattern with no intrinsic masses seen. She was commenced on tabs Tenofovir disoproxyl fumarate 300mg daily. Six months into her treatment, the HBV DNA dropped to 619IU/L and ALT was 30IU/L. Treatment remained uneventful until three years afterwards when her results showed undetectable HBV DNA. We subsequently requested for HBsAg quantification which was undetectable at <5IU/L, HBsAg was negative and anti-HBS was positive at 85.1IU/L. An assessment of immune clearance phase was made and her anti-viral therapy discontinued. She was however, continued on surveillance for HCC. **Conclusion**-Long-term treatment with nucleotide analogues may rarely, result in HBsAg loss.

Keywords: Hepatitis B virus, Immunological clearance, Nucleotide analogue.

INTRODUCTION

Infection with hepatitis B virus (HBV) remains an important global public health problem particularly in Sub-Saharan Africa with significant morbidity and mortality (Okonkwo, U. C. *et al.*, 2018). The main goal of therapy is to improve survival and quality of life by prevention of progression to liver cirrhosis and hepatocellular carcinoma (HCC) (Wu, C. Y. *et al.*, 2014). Long-term suppression of HBV replication represents the main endpoint of current treatment strategies, while HBsAg loss is an optimal endpoint (European Association for the Study of the Liver. 2017; Terrault, N.A. *et al.*, 2016; Malu, A. O. *et al.*, 2015). Nucleotide analogues with high barrier to resistance such as tenofovir disoproxyl fumarate (TDF), entecavir and tenofovir alenfenamide (TAF) are thought to be very effective in inducing long-term viral suppression but rarely HBsAg loss (Buti, M. *et al.*, 2016; Hosaka, T. *et al.*, 2013).

CASE REPORT

We report the case of a 56year old lady, who presented with a positive HBsAg result which was detected following a febrile illness. There was no history of jaundice or other symptoms referable to a liver disease. She was hypertensive and diabetic with good control.

Baseline evaluation showed that HBV DNA was 2099 iu/L, HBeAg was negative, ALT was 10 iu/L (ULN =12), Creatinine 0.76mg/dl (0.70-1.37), Albumin - 4.3mg/dl, Bilirubin- 0.26mg/dl. Haematocrit and platelets (12g/dl and 277 x $10^{9/L}$) were within normal limits. The aspartate-to-platelet ratio index (APRI) score was 0. 2 and it suggests insignificant liver fibrosis. She was Child-Pugh class A with a MELD score of 9. Ultrasound showed generalized increased echo-pattern and normal portal vein diameter with no intrinsic masses. She was commenced on tabs Tenofovir disoproxyl fumarate 300mg daily. Six

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months into her treatment, the HBV DNA dropped by >1 x $\log_{10}$ to 619 iu/L and ALT rose to 30 IU/L (ULN =12).

Treatment remained uneventful until three years afterwards when her results showed undetectable HBV DNA and normal ALT levels. We subsequently requested for HBsAg quantification which was undetectable at <5IU/L, HBsAg was negative and anti-HBS was positive at 85.1IU/L.

An assessment of immune clearance phase was made and her anti-viral therapy discontinued. She was however, continued on surveillance for HCC with six monthly abdominal ultrasound and alpha fetoprotein measurement.

DISCUSSION

The ideal end point of treatment for chronic HBV infection is sustained off-therapy HBsAg loss with or without sero-conversion to anti-HBs (European Association for the Study of the Liver. 2017; Terrault, N.A. *et al.*, 2016). Currently, two sets of treatments are available for the treatment of chronic HBV infection; the nucleoside/nucleotide analogs (NUCs / NAs) or PEGylated interferon (PEG IFN) (European Association for the Study of the Liver. 2017; Terrault, N.A. *et al.*, 2016; Malu, A. O. *et al.*, 2015). The goals of the treatment include: The induction of long-term suppression of HBV DNA levels which represents the main endpoint of all current treatment strategies, loss of HBeAg and development of anti-HBeAg antibodies in patients who were initially HBeAg positive, ALT normalization, improved histology; loss of HBsAg and the seroconversion to anti-HBS (European Association for the Study of the Liver. 2017; Kim, G. A. *et al.*, 2014; Marcellin, P. *et al.*, 2016).

Due to the high relapse rate after NAs treatment discontinuation, the current recommendation is to initiate treatment with a NA with a high degree of barrier to resistance such as TDF, TAF or entecavir (European Association for the Study of the Liver. 2017; Terrault, N.A. *et al.*, 2016). In patients with HBeAg-negative chronic hepatitis, long-term treatment until HBsAg loss is recommended. In HBeAg-positive CHB patients who achieve HBeAg seroconversion with undetectable HBV DNA, the relapse rates depend on the duration of consolidation therapy. Consolidation therapy of at least three years decreased the rate of relapse and increased the rate of HBsAg loss significantly (Marcellin, P. *et al.*, 2014; Buti, M. *et al.*, 2015).

The index patient was commenced on TDF because of elevated HBV DNA levels and subsequently developed HBV DNA suppression and HBsAg loss after 3 years of therapy. Although she initially developed flare of ALT, it later normalized. ALT flares is usually associated with induction of immune response and typically observed following treatment with pegylated interferon (Sonneveld, M. J. *et al.*, 2012).

Our observation is the first reported in Nigeria to the best of my knowledge. It is similar to what was reported by Marcellin *et al.*, (2014) in two phase 3 trials in Europe. In that study, patients with CHB on TDF were followed up for 8 years. They reported that TDF was associated with durable virologic response and no resistance with HBsAg clearance achieved in approximately 1% of the patients. Tenofovir alenfenamide (TAF), a prodrug of TDF was also found to show similar response after 96weeks of therpy (Agarwal, K. *et al.*, 2017).

Pegylated interferon through its immunomodulatory properties has been reported to induce cytotoxic T-cell activity and lead to immune clearance of the infected cells thus, reducing the covalently closed circular DNA (cccDNA) levels and higher albeit variable immunological response of 5-23%.[9] NAs have no effect on clearing the cccDNA. However, HBV DNA markedly gets suppressed with NAs treatment, and as a result, the body restores CD4 and CD8 cellular immune response against HBV which may ultimately result in immunological response with the loss of HBsAg antigen and the development of antibodies to the surface antigen.

CONCLUSION

Long-term treatment with nucleotide analogues may rarely, result in HBsAg loss.

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