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Case Report

Mechanisms and Treatment of Patients with Chronic Hepatitis B Presenting with Low-Level Viremia (LLV): A Case Report

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Abstract

Background: At this stage, CHB is mainly pursuing functional cure, which is defined as the completion of a limited course of treatment with persistent undetectable serum HBsAg and HBV DNA, HBeAg negativity (with or without HBsAg seroconversion), persistence of residual cccDNA, regression of hepatic inflammation, improvement of hepatic histopathology, and a significant reduction in the prevalence of end-stage liver disease, i.e., the end of treatment, and a significant reduction in the incidence of end-stage liver disease. An important modality for achieving clinical cure is currently combination therapy. However, in recent years, studies have found that some HBV-infected patients with LLV even after long term antiviral therapy, i.e., HBV-DNA levels are higher than the lower limit of detection but lower than 2000 IU / ml. Many experts believe that weak host immunity and the abundance of deoxynucleotides in the body leading to the competitive inhibition of the NUC is the main reasons. For chronic HBV patients who still have LLV even after more than 1 year of antiviral therapy, the treatment regimen should be modified when appropriate. In this article, we report a case of chronic HBV with LLV during antiviral therapy, and the study of the mechanism of LLV will help us to optimize the antiviral therapy and reduce the incidence of adverse effects such as cirrhosis and hepatocellular carcinoma.

Case Summary: Patients with chronic hepatitis B infection who develop LLV on sequential combination therapy and ultimately achieve clinical cure. The patient had been infected with the hepatitis B virus for 18 years and had recurrent liver function abnormalities for 7 years, and began receiving treatment 7 years ago, and was now suffering from liver function abnormalities, positive surface antigen and core antibodies, and was initially diagnosed with chronic viral hepatitis B. During the sequential combination therapy of Nas and PEG-IFN, the patient developed LLV. During the course of Nas and PEG-IFN sequential combination therapy, the patient developed LLV, and after adjusting the treatment regimen, the surface antigen and HBVDNA became negative, and clinical cure was achieved.

Conclusion: Some HBV-infected patients develop LLV during long-term antiviral therapy, which may be related to the competitive inhibition of NUC due to weak host immunity and abundant deoxynucleotides in the body, and the treatment regimen should be modified at an appropriate time for chronic HBV patients who suffer from LLV even after more than one year of antiviral therapy.

Keywords: HBV; Chronic Hepatitis B; Low-Level Viremia(LLV); Mechanisms of LLV; Sequential Combined Therapy; Clinical Cure; Case Report

Introduction

HBV infection is prevalent worldwide, with approximately 296 million people living with chronic HBV infection globally [1], of whom approximately 25% die from liver-related complications [2], and thus chronic HBV infection remains the leading cause of liver disease-related deaths worldwide. Nucleoside (acid) analogs (NAs) and Polyethylene Glycol Interferon Alpha (PEG-IFNα) are currently used as anti-HBV therapy, and there is more than sufficient evidence that both drugs are effective in improving the symptoms and prognosis of chronically HBV-infected patients [3]. Persistent or intermittent low levels of HBV DNA positivity (known as low-level viremia) are detected in the plasma of many patients after long-term standardized treatment with first-line antiviral drugs [4]. In recent years, it has been found [5] that Low-Level Viremia (LLV) occurs in approximately 30% of patients with CHB despite being on long-term NAs antiviral therapy. The 2018 American Association of the Society of Liver Diseases (AASLD) Guidelines [6] state that:LLV is defined as HBV DNA < 2000 IU/ml but is still detectable (minimum detection limit of detection is 10 IU/ml) in patients. This is becoming a major challenge in the treatment and management of Chronic Hepatitis B (CHB). As a result, the World Health Organization (WHO) has set a goal to eliminate HBV as a public health threat by 2030 [7]. This case report focuses on a case of LLV in a CHB patient who developed LLV during sequential combination therapy and discusses the mechanism of LLV emergence and the protocol for adjusting the treatment.

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Case Presentation

A 27-year-old man was admitted to the hospital with recurrent abnormal liver function. At the time of admission, there was no obvious discomfort. In August 2001, the patient was found to be positive for HBsAg, HBeAg, and HBcAb in a physical examination, but his liver function was normal, and he had no accompanying symptoms such as dyspepsia and malaise. In 2012, a review of his liver function was found to be abnormal, and he was given a short-acting IFN, which was ineffective, and then changed to ETV antiviral therapy, while he was given liver-protecting medications for symptomatic treatment. The review of his liver function was repeated in 2019, and the liver function was abnormal again. Liver function was abnormal again: ALT 50 U/L, AST 51 U/L; Hepatitis B penta: HBsAg 255.35 IU/ml, HBsAb 5.32 mIU/ml, HBeAg 0.14PE IU/ml, HBeAb 1.15S/CO, HBcAb 10.46S/CO; HBV-DNA: lower than the lower line of detection (< 500 IU/ml). Liver puncture biopsy: the structure of hepatic lobules was basically normal, hepatocytes were mildly edematous and degenerated, there was a small amount of lymphocyte infiltration in the confluent area, and there was no hyperplasia of small bile ducts and fibrous tissues. Pathologic diagnosis: mild chronic hepatitis, G1S0.

The patient's vital signs were stable, with no yellow staining of the skin and mucous membranes, no hemorrhagic spots, and a flat and soft abdomen without pressure or rebound pain; the liver and spleen were not palpated under the ribs, and there was no percussion pain in the hepatic area, and the turbidities of mobility were negative. His family members were in good health, no HBV-positive persons, and no family

history of hereditary disease. The patient was diagnosed with chronic hepatitis B and given sequential combination therapy with ETV and PEG-IFN. At 12 weeks of treatment, HBV DNA turned positive, LLV, and the treatment was adjusted to the combination of TAF and PEG-IFN. At 61 weeks of treatment, HBsAg turned negative and anti-Hbs turned positive, TAF was discontinued, and PEG therapy was continued. At 119 weeks of treatment, HBV DNA was negative and PEG-IFN was discontinued, at which point clinical cure was achieved by persistent undetectable serum HBsAg and HBV DNA, HBeAg negativity (with or without HBsAg seroconversion), persistence of residual cCCDNA, subsidence of hepatic inflammation, improvement of hepatic histopathology, and a significant reduction in the incidence of end-stage liver disease.

Discussion

With the improvement of the sensitivity of HBV DNA detection, low levels of HBV DNA (HBV DNA < 2000 IU/mL, LLV) are being detected continuously or intermittently in an increasing number of patients during antiviral therapy. In our case, LLV was present at 12 weeks of combination therapy with ETV and PEG-IFN. Currently, there is no recognized definition of LLV at home and abroad. The 2018 American Academy of Liver Diseases (AASLD) guideline [8] states: LLV is defined as patients with HBV DNA < 2000 IU/ml, but still detectable (minimum detection limit of 10 IU/ml). Lu Fengmin et al [9] experts suggested that chronic HBV-infected patients who received first-line drugs such as ETV, TDF or TAF for at least 48 weeks, and whose serum HBV DNA was still detectable by sensitive qPCR (minimum detection limit of 20 IU/ml or 10 IU/ml) but < 2000 IU/ml, after exclusion of influences such as medication adherence and viral drug-resistance mutations were Patients are defined as LLV. In the clinical diagnosis of LLV, factors causing fluctuations in HBV DNA (e.g., omission of antiviral medications, reduction in the dose of medication, inappropriate use of medication, etc.) should be excluded. Drug-drug and drug-food interactions may also affect the antiviral effects of NUC [10]. Viral detectability caused by cross-resistance, locus mutation or sample contamination should also be excluded [11].

The stable presence of HBV ccc DNA in the nucleus of infected hepatocytes is the key to the chronicity and intractability of HBV infection [12,13]. ccc DNA is sourced by 2 pathways, including initial infection and intracellular replication backfill [14]. after HBV entry into the hepatocyte, viral nucleocapsids carry the HBV relaxed circular DNA (rcDNA) into the nucleus of the hepatocyte, which is converted to cccDNA by the host DNA repair system into cccDNA. meanwhile, pre-genomic RNA (pgRNA) (core antigen and P-protein mRNA) is transcribed from cccDNA, and pgRNA can be used as a reverse transcription template to form new rcDNA [15]. On the one hand, newly synthesized rcDNA can be packaged into intact viral particles to infect new normal hepatocytes. On the other hand, rcDNA can also enter the nucleus and replenish the cccDNA in the nucleus after repair to maintain the stability of the cccDNA library in the nucleus of hepatocytes. The main mechanism of NUC antiviral activity is to inhibit the synthesis of progeny viral rcDNAs by competing for binding of P proteins with dNTPs in the cell. However, in the presence of large amounts of dNTP, NUC does not completely inhibit HBV replication and prevents cccDNA formation in newly infected hepatocytes [16,17]. Thus, NUC is unable to completely block DNA strand synthesis. This results in persistent or intermittent serum levels of HBV DNA above the limit of detection in some antiviral-treated patients exhibiting LLV.

Elevation of ALT in patients treated with NAs reflects the extent of hepatocellular injury, and its elevation is associated with a more pronounced decrease in serum HBV DNA load [18], suggesting that patients with some degree of hepatic inflammatory activity tend to respond better to NAs antiviral therapy. Similarly, patients with high hepatic inflammatory activity (G ≥ 2) had more pronounced decreases in serum HBV DNA and HBeAg 6 months after antiviral therapy was initiated compared to patients without significant hepatic inflammation (G < 2) at baseline. In addition to this, the reduced expression of NTCP and the significant down-regulation of cell membrane localization in hepatocytes proliferating as a result of inflammatory activity are also detrimental to HBV reinfection [19]. However, several studies have shown that in many patients with chronic hepatitis B, there is a decrease in the number of CD8+ T cells and CD4+ T cells, an imbalance in the function of regulatory T cells [20-22], and a significant increase in the proportion of Treg cells in the peripheral blood, and a positive correlation between the proportion and the number of Treg cells and the amount of serum HBV DNA [23], factors that lead to low cellular immunity in the patients.B cells can produce HBsAb, which has an important role in HBsAg clearance, reducing viral load in vivo, and eliminating infected cells [24-26]. In patients with chronic HBV infection, the overall peripheral B cells are activated and dysfunctional, and only very few anti-HBs-secreting B cells are detected [27], which leads to a severe decline in the humoral immune function of patients. Patients with weakened immune function have mild active inflammatory injury that cannot induce clearance of infected hepatocytes, and low proliferative state hepatocytes are susceptible to HBV infection and facilitate effective HBV replication, and cccDNA accumulation occurs, leading to prolonged persistence of ccc DNA, which is conducive to the development of LLV [28-30].

Several studies have demonstrated that autophagy plays a key role in HBV replication and pathogenesis [31-32], and that cellular autophagy is an important process that regulates the HBV life cycle by modulating HBV transcription, assembly, and release. IFNα-2a interferes with a variety of intracellular signaling pathways, including inhibiting the Akt/mTOR and AMPK signaling pathways, facilitating autophagosome formation, and blocking autophagic degradation [33]. The PI3K/AKT/m TOR signaling pathway has been shown to be a major pathway in the cellular regulation of autophagy. mTORC is directly involved in the regulation of the activities of major cellular autophagy proteins, and its upstream regulator is only the PI3K/AKT axis, which is capable of integrating signaling pathways from the cellular environment and ultimately regulates the cellular autophagic response [34]. This effect of IFNα-2a leads to HBV replication Enhancement.

According to the available guideline recommendations, AASLD suggests that LLV (< 2000 IU/ml) patients receiving ETV or TDF/TAF monotherapy continue monotherapy, regardless of ALT; whereas antiviral therapy is not recommended for patients with inactive CHB without cirrhosis who are HBeAg-negative, have normal ALT activity and HBV DNA < 2000 IU/ml [35]. However, the level of evidence for the above recommendations is low. Whereas the European Association for the Study of the Liver, EASL, does not recommend changing the initial treatment strategy for patients with HBV DNA < 69 IU/ml in an attempt to further reduce the HBV DNA level, but if the HBV DNA is between 69 and 2,000 IU/ml, it is possible to consider the possibility of switching to another drug or ETV+TDF/TAF combination therapy [36].

A retrospective study in China found that LLV patients who changed their treatment regimen were more likely to achieve complete virologic suppression and have a better long-term prognosis than those who continued their original regimen [37]. In a study conducted by Li, et al [38] to evaluate the efficacy and safety of switching the treatment regimen from ETV to TAF in LLV patients, after 24 weeks of treatment, the rates of complete virologic response in the TAF group (75 patients) and the ETV group (75 patients) were 62.7% and 9.3%, and the rates of ALT reversion were and 47.6% and 10.5%, respectively, which were both significantly higher in the TAF group than in the ETV group. This also suggests that in ETV-treated LLV patients, switching to TAF therapy is effective for HBV suppression and normalization of liver function compared to continuing ETV monotherapy. In a study by Yin, et al [35], it was suggested that increasing the dose of ETV may be a viable option for LLV patients receiving ETV monotherapy.

In a prospective study in real-world clinical practice, switching to TAF was superior to continuing ETV monotherapy in patients with LLV, and this change helped to control the progression of hepatic fibrosis or promote its reversal and reduce the risk of HCC. Results of a study comparing the efficacy of 2 combination regimens of polyethylene glycol interferon (Peg-IFN)+NAs and NAs+NAs in treating patients with HBeAg-

negative LLV showed that both regimens were effective in suppressing viral replication, but the Peg-IFN combination regimen had a higher 48-week complete virologic response rate and an HBsAg clearance/serological conversion rate of 30.9%. HBeAg-negative patients who discontinued NUC may have a higher serum clearance of HBsAg compared to those who continued NUC, suggesting that timely discontinuation of NUC may have a greater probability of achieving a functional cure. In the present case, this patient with mild chronic hepatitis B, who developed LLV on combination therapy with ETV and PEG-IFN, adjusted ETV to TAF to continue treatment in combination with PEG-IFN, and with the combined inhibition of HBV replication and transcription by the two drugs, HBsAg turned negative and anti-Hbs turned positive at 61 weeks of treatment, and his treatment resulted in a serologic response, with HBV DNA remaining PEG-IFN was discontinued, and PEG-IFN was continued. Under the dual effects of antiviral and immune modulation, HBV DNA turned negative and a complete virological response was obtained, and PEG-IFN was discontinued, achieving clinical cure.

Conclusion

At the present stage, the treatment of chronic hepatitis B mainly adopts a combination of NAs and IFN regimen, and in the course of its antiviral treatment, more and more patients develop LLV, and a large number of studies have shown that the LLV status is detrimental to the long-term clinical outcome of chronic HBV-infected patients. The emergence of LLV may be attributed to the following reasons: deoxynucleotide abundance leading to competitive inhibition of the NUC, weak host immunity, and interference of IFN with the intracellular signaling pathways. The control and treatment of LLV has become an urgent problem, and is now mainly treated by switching to or adding potent low-resistant NAs, or combined with Peg-IFN.

Data Availability Statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics Statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Informed Consent Statement

Informed consent was obtained from the patient.

Author Contributions

Jun Lv provided case information and reviewed and revised the article; Lin Wang reviewed the literature and contributed to the drafting of the manuscript. All authors contributed to the article.

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