COMBINED CORTICOSTEROIDAND ANTIVIRAL THERAPY FOR HEPATITIS B VIRUS - RELATED ACUTE LIVER FAILURE: A REPORT OF THREE PATIENTS

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ABSTRACT

Hepatitis B virus is one of the most common causes of liver failure in the world. Hepatitis B virus-related acute liver failure (HBV-ALF) may occur after acute hepatitis B or acute exacerbation of chronic hepatitis B. HBV-ALF can result in high mortality. HBV-ALF can be due to an overwhelming response of the immune system to hepatitis B virus.

Antiviral therapy with nucleos(t)ide analogues has an important role and is recommended in ALF due to severe acute hepatitits B as well as acute exacerbation of chronic hepatittis B but their effect is still limited. Therefore, a combination of antiviral and immunosupressive therapies in theory is resonable.

We reported three patients with ALF related to acute or acute exacerbation of chronic hepatitis B who were successfully treated with antiviral therapy combined with corticosteroids.

Keywords: *Acute liver failure, hepatitis B, corticosteroids, nucleos(t)ide analogues*

I. INTRODUCTION

Hepatitis B is one of the leading causes of liver failure in the world. Acute hepatitis B and acute exacerbation of chronic hepatitis can lead to ALF with significant mortality. HBV-ALF is thought to be due to an overwhelming immune response to the virus and does not appear to be related to the viral load or the rate of viral replication. In fact, many patients with hepatitis B might have very high viral load but normal liver enzymes and little or no inflammatory activity in the liver. Conversely, in fulminant or chronic hepatitis B, viral load may be reduced to either low or negative levels while hepatitis and liver failure continue to progress [8], [13], [18].

Nucleoside (t) ide antiviral therapy has been shown to play an important role in the treatment of active chronic hepatitis and in the majority in chronic hepatitis B infection. Although there have been some consensus recommendations for the use of antiviral drugs with high barrier to resistance including tenofovir, entecavir, their role in the treatment of ALF due to acute exacerbation of chronic hepatitis B or fulminant hepatitis B has not been well established. A significant proportion of patients die from liver failure despite a very low or negative viral load [1], [12], [17], [19].

In HBV-ALF, in addition to rapid control of the virus, further measures are required to limit the overwhelming immune response causing hepatic injury and hepatic failure. Therefore, a combination of antiviral therapy and immunosuppressive drugs is theoretically reasonable. In this article, we reported three cases with favorable response to the combination of antiviral therapy and corticosteroids after treatment failure with conventional antiviral therapy.

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II. CASE REPORT

1. Patient Nguyen Cao X.P, 26 years old, was hospitalized on 23/02/2018. He presented two weeks before hospitalization with jaundice and fatigue. He had been treated at other hospital but did not improve. The results of her laboratory tests were as followed: HBsAg (+), HBeAg (+), Anti HBc IgM (+), Anti HAV IgM (-), AST: 181 UI/L, ALT: 448 UI/L, total bilirubin: 417 mcmol/L, HBV DNA (-). He was diagnosed with fulminant hepatitis B and continued treatment with entecavir 0.5 mg as previously prescribed. Her condition continued to deteriorate after 3 days with worsened jaundice and total bilirubin level of 538 mcmol/L, HBeAg (-), AntiHBe (+). His INR level was within normal limits during hospitalization. Additional treatment with intravenous prenisolone 1.5mg /kg/day was indicated, which resulted in rapidly lowered bilirubin and liver enzymes within 3 days after treatment. He continued his treatment with oral prednisolone at 1 mg/kg, with gradual reduction in dose by 10 mg/week and complete cesation of corticoid therapy after one month. Testing revealed complete seroconversion after 3 months with HBsAg (-), anti HBs (+), normal biochemistry test results. He stopped taking entecavir afterwards

2. Patient Nguyen Van C, 23 years old, was hospitalized on 7/3/2018. He also presented two weeks before hospitalization with fatigue and jaundice. He had a history of untreated hepatitis B which was detected 5 years ago. His laboratory results were as followed: HBsAg (+), HBeAg (-), Anti HCV (-), Anti HAV IgM (-), HBV DNA 1.65 x 10^3/mL, AST 22600 UI/ mL, ALT 8019 UI/mL, total bilirubin 511 mcmol/L, INR 1.07. He was diagnosed with acute exacerbation of chronic hepatitis B and treated with tenofovir 300 mg/day. After 3 days, the bilirubin level continued to increase with total bilirubin of 789 mcmol/L, AST 512 UI/L, ALT 2893 UI/L. His bilirubin continued to increase to 997 mcmol/L. He developed hepatic encephalopathy with headache, irritability, nausea, vomiting, and confusion. He was prescribed with intravenous prednisolone 1.5 mg/kg but treatment was discontinued after five days because of fever which might be due to superinfection. However, his condition improved dramatically with a rapid decrease in bilirubin, jaundice, fever and symptoms of hepatic encephalopathy after one week of treatment. He was discharged and continued his antiviral treatment with tenofovir. After two months, his follow-up laboratory test showed normal liver enzyme and bilirubin, HBV DNA (-) and HBsAg (+). Maintenance therapy with tenofovir was continued.

3. Patient Nguyen Thi T, 54 years old, was hospitalized on April, 23rd, 2018. She presented with a 10-day history of increasing fatigue and jaundice. She had a history of chronic hepatitis B treated with a medication which she could not recall its name and the treatment was interupted by the patient. Her laboratory tests showed HBsAg (+), HBeAg (+), Anti HCV (-), Anti HAV IgM (-), AST 817 UI/L, ALT 66 UI/L, total bilirubin 327 mcmol/L, HBV DNA 9.89 x 10^8/L, INR 1.49. Her initial treatment was entecavir 1 mg daily. She did not response to the initial treatment and the bilirubin level continued to increase after 10 days with total bilirubin 409 mcmol/L, AST 110 U/L and ALT 117 U/L. She was given prednisolone 1.5 mg/kg/day IV for one week in addition. Bilirubin decreased to 259 mcmol/L after five days of treatment. Then, she switched to oral prednisolone 1 mg/kg with gradual decrease in dose by 10 mg/week. Prenisolone was stopped completely after 1.5 months. At two-month follow-up, her bilirubin and liver enzymes returned to normal limits. After three months, HBV DNA became negative but HBsAg remained positive. She was put on maintenance therapy with entecavir.

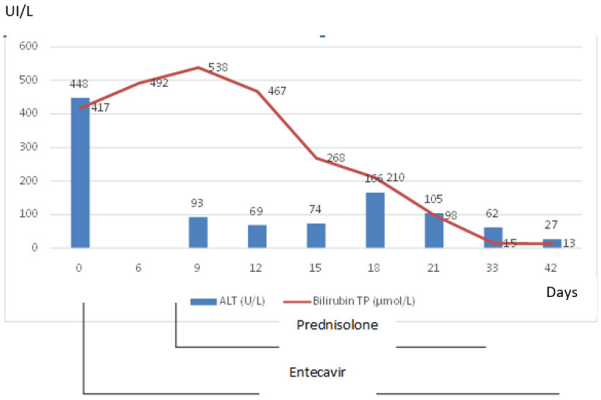

Chart 1. Patient Nguyen Cao X.P

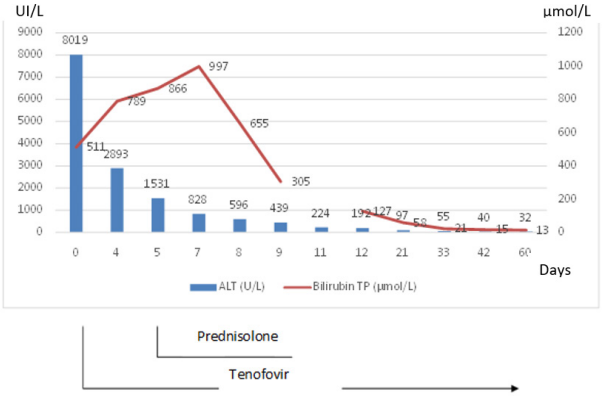

Chart 2. Patient Nguyen Van C

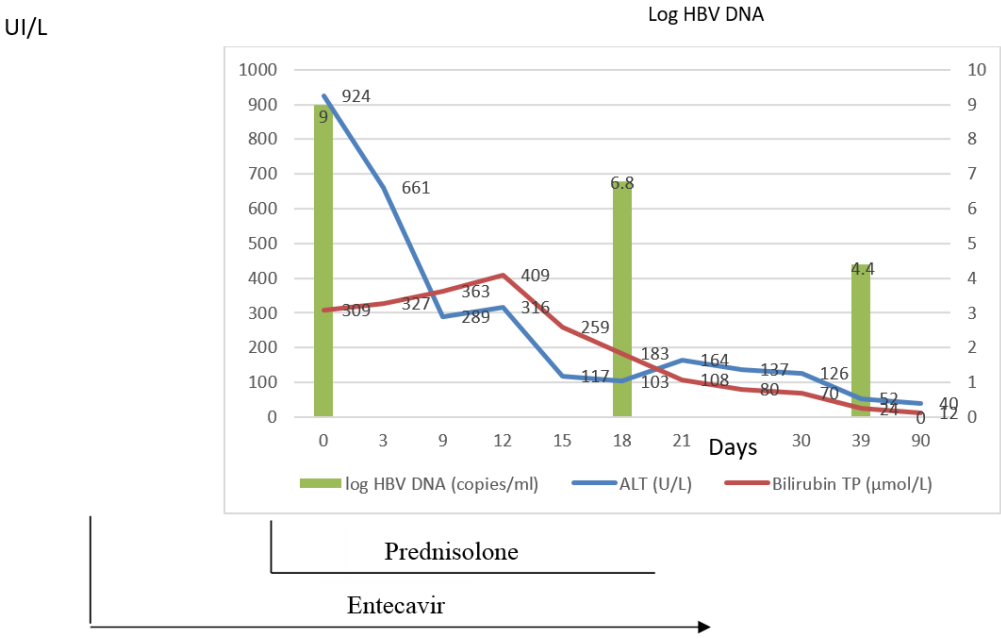

Chart 3. Patient Nguyen Thi T

III. DISCUSSION

HBV-ALF is a serious clinical condition with very high mortality. There has been no significant progress in the treatment of HBV-ALF except for liver transplantation. According to the Asian Pacific Association for the Study of Liver (APASL), acute liver failure is defined as an acute liver injury with jaundice, coagulopathy (INR> 1.5), ascites or hepatic encephalopathy within 4 weeks after the onset of disease in patients previously diagnosed with or without chronic liver disease [14].

HBV-ALF can occur in fulminant hepatitis B or acute exacerbation of chronic hepatitis B. This is an immune response which involves the interaction between hepatitis B virus, hepatocytes, and immune cells. When an overwhelming immune response occurs, it causes severe, rapid hepatolysis in large quantities leading to acute liver failure. Acute liver failure in acute excacerbations of chronic hepatitis B may occur randomly or in patients receiving longterm immunosuppressive therapy without concurrentanti viral therapy [2], [11], [13]] [20]

In terms of pathogenesis, a number of preliminary studies have demonstrated the active involvement of T-lymphocytes in acute hepatitis as well as acute exacerbation of chronic hepatitis. This is a consequence of the innate immune response and the adaptive immune response with viral replication

including HLA type I, cytotoxic T-lymphocyte (CTL) – mediated immune cytolysis of HBV antigen(s) expressing hepatocytes. Macrophages, cytokines 2, 4, 6, 10, etc., may also be present. However, the underlying mechanism of the overwhelming response causing acute liver failure is yet to be clarified [6], [8], [11].

The question is whether immunosuppressants should be used to treat acute or acute-on-chronic hepatitis B with acute liver failure. There have been several studies showing that corticosteroids have the potential to improve survival in these patients [2], [21]. However, some other studies showed the opposite results. Recent consensus of various associations for study of liver disease do not mention the role of corticosteroids in the treatment of HBV-ALF [1], [14], [15], [19].

An acute exacerbation of chronic hepatitis B usually follows a reactivated infection with a sudden increase in HBV DNA and ALT levels. The clinical course of an acute exacerbation can be divided into four stages according to the change of HBV DNA level. In the ascending phase, stage I is characterized with HBV DNA $<10^5$ coppies/mL while phase II is denoted by HBV DNA $> 10^5$/mL. In the descending phase, HBV DNA$> 10^5$/mL represents stage III and stage IV is characterized with HBV DNA $<10^5$/mL. Patients in stage I is unlikely to be symptomatic. Therefore, patients usually present in stages II, III, and IV. In stage IV, the immune response has been activated and and amplified maximally which results in rapid decrease in HBV DNA level. Hence, the effect of antiviral therapy at this stage is expected to be insignificant [6], [18].

The study by Lospez Velazque J demonstrated that a level of total bilirubin over 3.45 mg/dL in the first week of hospitalization of HBV-ALF had a higher predictive value of mortality rate than MELD or Child-Pugh scores. The high level of bilirubin results in rapid deterioration of liver function as well as other target organs [10].

In acute liver failure, impaired hepatic function limits the conjugation of indirect bilirubin. In addition, in HBV-ALF, bile excretion is impaired due to cholestasis.Therefore, direct bilirubin, which is toxic to hepatocytes, is accumulated in the liver as well as in the blood, causing liver failure with the first manifestation of jaundice. When bilirubin level rises to more than 350 mcg/dL, patients are at increased risk of mortality from irreversible liver failure [7], [10]. A study by Chan H.L found that the risk factors of high mortality were low platelet count and elevated bilirubin. [5]

In fulminant hepatitis B, HBV DNA and HBeAg will become negative when there is an evidence of severe liver failure due to an overwhelming immune response [11], [14]. This can be clearly seen in patient 1: although HBV DNA was negative at admission, patient continued to experience liver damage and liver failure with increasingly elevated liver enzymes and bilirubin higher than admission levels. The antiviral therapy was almost no longer effective since the viral load had become negative.

In acute hepatic failure in chronic hepatitis B, a rapid reduction in bilirubin level after seven days has a prognostic value of favorable response to corticosteroids and a reduction in mortality after 3 months [9]. This was apparent in all three patients with a rapid reduction in bilirubin level within 3 days of corticosteroid therapy.

Controversies still exist concerning various criteria in the definition of acute liver failure in hepatitis B. The Asian Pacific Association for the Study of the Liver (APASL) definition includes jaundice, INR> 1.5, and signs of hepatic encephalopathy and time of occurrence within 4 weeks of onset. The European Association for the Study of the Liver (EASL) offers the diagnostic criteria with less rigorous conditions: acute liver failure is diagnosed with evidences of acute liver injury, at least 2-3 folds increase in liver enzymes, evidences of liver failure such as jaundice and coagulopathy disorder within the first 10-30 days of onset of disease. EASL does not consider coagulopathy and hepatic encephalopathy as mandatory criteria since INR testing techniques

have not been standardized among laboratories and signs of hepatic encephalopathy can sometimes bevery ambiguous and difficult to evaluate, andare apparentonly in later stages of disease.

Meanwhile, the Chinese Society of Hepatology-emphasizes on the significance of bilirubin level > 10 mg/dL (170 mcmol/L) and rate of bilirubin increase of > 1 mg/day [1], [14], [21]. In our report, significantly elevated bilirubin was seen in all three patients while there were no significant changes in coagulation results (INR) and hepatic encephalopathy was seen in only one patient. This might be related to the genotype and geographic distribution of hepatitis B virus. Genotype B of hepatitis B virus is very common in East and Southeast Asian countries including China, Japan and Vietnam. This genotype causes hepatitis and acute liver failure with elevated liver enzymes and bilirubin, which are clinically manifested as rapidly increased jaundice [4], [16]. Due to the high risk of hyperbilirubinemia-induced irreversible liver failure, we decided to use corticosteroids after gaining consent from patients and their relatives without waiting for signs of coagulopathy (INR) and hepatic encephalopathy.

There was a variation in viral load among three patient. While HBV DNA was negative in patient 1 and was low (10^3 copies/L) in patient 2, it was significantly elevated in patient 3 (10^8 copies/L). In patient 1 with fulminant hepatitis,the overwhelming immune responses may rapidly decrease the viral load to negative level. In patient 2 who was admitted two weeks after onset of disease, the immune response was also very powerful with signs of severe liver insufficiency including elevated bilirubin and hepatic encephalopathy. This powerful immune response also suppressed viral replication and brought the viral load to a low level. In patient 3 who was hospitalized one week after disease onset, the viral load was sigficantly elevated which signified that the antiviral therapy had not been effective. Therefore, HBV DNA levels did not correspond to the intensity of immune response in these patients [2], [18].

The duration of corticosteroidtreatment ranged from 5 days to 45 days. Studies showed that a short-term 5-day treatment with dexamethasone and antiviral therapyimproved liver function and survival in patients with HBV-ALF [3]. The majority of other studies reported longer duration of corticosteroid treatment but not exceeding two months. This demonstrated that the immune response in patients with HBV-ALF was induced by viral replication but seemed independent of viral load and couldbe controlled rapidly by corticosteroid.

IV. CONCLUSION

Corticosteroids helped improve acute liver failure due to acute hepatitis B and acute exacerbation in chronic hepatitis B in three reported patients. The duration of corticosteroid treatment was short, ranging from 5 days to 1.5 months.

There was a strong immune response in all three patients and corticosteroid therapy play an important role in suppressing the immune response.

The main presentation of HBV-ALF was significant elevation of bilirubin. This is probably due to the geographic distribution of hepatitis B virus genotype.

A sufficiently large studies is required to adequately assess the efficacy of treatment for HBV-ALF using combined antiviral with corticosteroid therapy.

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