Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Hepatitis B flares in chronic hepatitis B: Pathogenesis, natural course, and management

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Summary

Hepatitis B flare, defined as an event with abrupt rise of alanine aminotransferase (ALT) levels to >5 times the upper limit of normal during chronic hepatitis B virus (HBV) infection, is considered to be the result of a human leukocyte antigen-I restricted, cytotoxic T lymphocyte mediated immune response against HBV and its downstream mechanisms. It may occur spontaneously, during or after antiviral therapy and in the setting of immunosuppression and/or chemotherapy. The clinical spectrum of hepatitis B flares varies from asymptomatic to symptomatic and typical overt acute hepatitis, even with hepatic decompensation or failure. Flares may also occur in viraemic patients with cirrhosis with higher incidence of decompensation/mortality, hence requiring immediate antiviral therapy. An upsurge of serum HBV DNA and hepatitis B surface antigen levels usually precedes the abrupt rise of ALT levels. Rising or stable and high HBV DNA during flares represent ineffective immune clearance and further hepatocytolysis, even hepatic decompensation, may occur. Such patients require immediate antiviral therapy. In contrast, bridging hepatic necrosis and/or alpha-fetoprotein levels >100 ng/ml or decreasing HBV DNA during flares represent a more effective immune clearance and frequently leads to seroclearance of HBV DNA and/or hepatitis B e antigen with remission. If patients are non-cirrhotic and there is no concern of developing decompensation, patients may be observed for 3–6 months before deciding on the need of antiviral therapy. Severe and repeated flares are prone to develop into decompensation or lead to the development of cirrhosis, thus a timely treatment to prevent the hepatitis B flare is better than to cope with the flare. Screening, monitoring and prophylactic or pre-emptive antiviral therapy is mandatory for patients who are going to receive immunosuppressants or chemotherapy.

Keywords: Alpha-fetoprotein; Chemotherapy; Cirrhosis; Hepatitis B virus; Hepatocellular carcinoma; Immune clearance; Immune restoration; Interferon-α; Nucleos(t)ide analogue; Pregnancy.

Received 24 June 2014; received in revised form 22 August 2014; accepted 24 August 2014

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Abbreviations: ADV, adefovir; AFP, alphafetoprotein; ALT, alanine aminotransferase; anti-CD_{20}, CD_{20} antibodies; anti-TNF, anti-tumour necrosis factors; ART, antiretroviral therapy; BHN, bridging hepatic necrosis; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; CTL, cytotoxic T lymphocyte; ETV, entecavir; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IFN-α, interferon alpha; IFN-γ, interferon gamma; LAM, lamivudine; Nuc, nucleos(t)ide analogue; Peg IFN, pegylated interferon; Treg, regulatory T cell; ULN, upper limit of normal; TDF, tenofovir.

Introduction

Chronic hepatitis B virus (HBV) infection is a dynamic state of interactions among HBV, hepatocytes and immune cells of the host. Accordingly, hepatitis activity with alanine aminotransferase (ALT) elevation and episodic abrupt rise of ALT, so called acute exacerbation or hepatitis flare, may occur spontaneously [1]. Hepatitis B flares may also occur during or after antiviral therapy or in the setting of immunosuppression and/or chemotherapy [2]. Based on earlier findings that less active hepatitis usually has an ALT level below 5 times the upper limit of normal (ULN), while active hepatitis has an ALT value far above this level [3], a chronic hepatitis B (CHB) flare was initially defined as "an abrupt elevation of ALT over 300 U/L (normal <40 U/L) in patients with a baseline ALT level <200 U/L (<5× ULN)" [4]. Later, it was defined as "an abrupt elevation of serum ALT to >5× ULN or a greater than 3-fold increase in ALT, whichever was higher" [5], and then as "intermittent elevations of aminotransferase activity to more than 10 times ULN and more than twice the baseline value" [6]. All of these definitions agree that "an abrupt ALT elevation >5× ULN" is the minimum criterion of a hepatitis flare. This ALT threshold has been widely accepted in the categorical analyses of therapeutical trials or clinical studies since 1990s. Acute superinfection with other hepatitis virus(es) in patients with chronic HBV infection also presents with an abrupt high rise of ALT and should be differentiated from the hepatitis flare caused by HBV (hepatitis B flare) using serologic or virologic assays [2,3,7].

In recent decades, ultrasensitive assays for serum HBV DNA and hepatitis B surface antigen (HBsAg) levels as well as new therapeutic agents have become available. Hence, new advances in the understanding of the natural history, the immunopathogenesis of the hepatitis B flare and its management have emerged. The following is an update and appraisal of the issues related to

hepatitis B flare, using a diagnostic threshold of ALT >5x ULN. The superinfection issues are not covered in this review.

Key Points

- Acute hepatitis B flares (ALT >5x ULN) are results of a HLA-I restricted, CTL mediated response against HBV. Stronger endogenous immune responses result in more hepatocytolysis, higher ALT levels and more effective clearance of HBV
- Flares with rising and high HBV DNA may lead to hepatic decompensation, thus requiring immediate antiviral therapy for prevention or rescue
- While flares in cirrhotic patients always require immediate antiviral therapy, flares in non-cirrhotic patients with decreasing HBV DNA may be followed by HBV and/or HBeAg loss with remission, and therefore, may be observed for 3-6 months for real indication of antiviral therapy
- Severe flares (decompensation, bridging hepatic necrosis, AFP >100 ng/ml) are prone to progress to cirrhosis, thus timely treatment to prevent the hepatitis flare is better than to treat the flare
- Screening, monitoring and prophylactic or pre-emptive antiviral therapy is mandatory for patients who are going to receive immunosuppressants or chemotherapy

Spontaneous hepatitis B flare

Clinical and pathological presentations

During the natural course of chronic HBV infection, hepatitis B flares start to occur during the hepatitis B e antigen (HBeAg) positive immune clearance phase [1,4,5,8]. Hepatitis B flares also occur in the HBeAg-negative reactive phase, but less frequently than during the HBeAg-positive phase [9–11]. In a hospital based study of CHB, the annual incidence of hepatitis flares was calculated to be 27% in 358 HBeAg-positive patients and 10% in 279 HBeAg-negative counterparts during a mean follow-up period of 2 years after entry [9]. It is not uncommon to have multiple episodic hepatitis B flares in one individual patient [4,8,11].

Clinical presentations

The clinical spectrum of hepatitis B flares varies from totally asymptomatic to symptomatic and to a feature similar to overt acute hepatitis (around 30%), with extreme manifestations of severe flares complicating hepatic decompensation (jaundice and coagulopathy) or even leading to hepatic failure [8–12]. Some hepatitis B flares may present as overt acute hepatitis, seropositive for HBsAg but negative for IgM class antibody to the hepatitis B core antigen (IgM anti-HBc) in patients who have had no past history of HBV infection or liver disease [13]. Hepatitis B flares may also occur in viraemic CHB patients with cirrhosis, including those after curative resection of hepatocellular carcinoma (HCC), and are associated with a higher rate of hepatic decompensation (13.9% *vs.* 2–3% in CHB) and mortality than in those of CHB without cirrhosis [14].

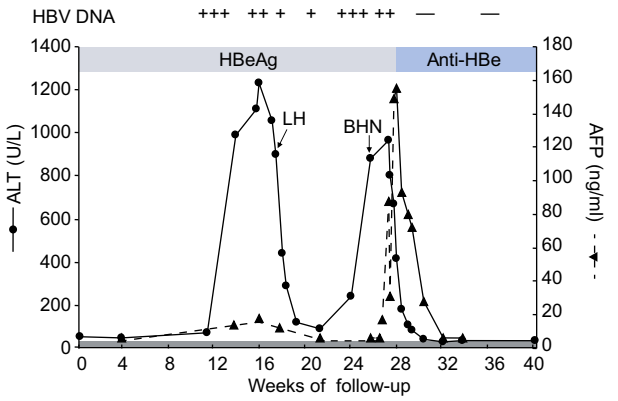

Fig. 1. Clinical course of a patient with two episodes of hepatitis flare. The abrupt elevation of serum alanine aminotransferase (ALT) is followed by a rise of serum alphafetoprotein (AFP), with a time lag of 1–2 weeks between the peak levels of ALT and AFP. AFP level was low during the flare with lobular hepatitis (LH) but >100 ng/ml during the (second) flare with bridging hepatic necrosis (BHN), which was followed by subsequent HBeAg seroconversion to its antibody (anti-HBe).

Laboratory findings and AFP level

The biochemical abnormalities, including serum ALT and bilirubin, of hepatitis B flares are similar to but in general less severe than those of acute hepatitis or acute superinfections [3]. Using enzyme immunoassay, 10–25% of hepatitis B flares were seropositive for IgM anti-HBc, but usually at a low serum/cut-off ratio compared to acute hepatitis B [8,11,15]. About 25–30% of hepatitis B flares are associated with an elevation of serum alpha-fetoprotein (AFP), of which the peak level is determined by 3 to 4 weekly or biweekly measurements after the onset of abrupt ALT elevation (Fig. 1). The peak serum AFP levels usually appear 1–2 weeks after the peak of ALT and may increase even over 2500 ng/ml, and usually return to a normal level within 3–12 months after the flare [16]. Of note, HCC should always be ruled out in patients with any elevated AFP level.

Histological findings

Liver biopsies during hepatitis B flares invariably show lobular necroinflammatory changes, which are distributed unevenly and may be so extensive that bridging hepatic necrosis (BHN) may occur [4,8,9]. BHN is evident in more than 80% of the patients with AFP >100 ng/ml during hepatitis B flares [7]. It was further demonstrated that patients with high AFP or BHN during the hepatitis flare had a high degree of AFP-producing oval cell activation (23.7–25.7% of hepatocytes), in contrast to 2.4–5.6% in patients with APF <100 ng/ml or no BHN [17]. Therefore, properly measured AFP-levels during the hepatitis flare of >100 ng/ml can be used as a surrogate marker of BHN.

Pathogenesis of the hepatitis B flare

HBV is not directly cytopathic by itself and the hepatocellular injuries are considered to be the results of a complex interplay among HBV, hepatocytes and immune cells of the host [1–4,7]. It has been documented by weekly to monthly assays that there is an upsurge of serum HBV DNA prior to the abrupt elevation of ALT [18–20]. There is also a parallel elevation of the serum HBsAg level along with the upsurge of serum HBV DNA (Fig. 2). Using a