Should chronic HBV infected patients with normal ALT treated: debate

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Abstract Alanine aminotransferase (ALT) levels have traditionally been used for treatment decisions in chronic hepatitis B virus (CHBV) infected patients. But recent data have raised doubts on this wisdom, as a significant proportion of CHBV infected patients with normal ALT have high HBVDNA levels and significant liver injury at presentation especially in areas of intermediate to high endemicity. A normal ALT value only identifies patients less likely to respond to current treatments, rather than patients who are not in need of the treatment. Patients with CHBV infection with normal ALT should be considered for treatment based on the HBV DNA levels and histological injury.

Keywords Chronic Hepatitis B · ALT

Introduction

Chronic hepatitis B currently affects about 400 million people, particularly in developing countries, and is responsible for 5,00,000–1.2 million deaths annually from liver cirrhosis and hepatocellular carcinoma (HCC) [1]. It is one of the most common infectious diseases among the world's leading causes of death.

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Phases of chronic HBV infection

It has become clear that HBV replication persists throughout the course of chronic HBV infection, host immune response plays a pivotal role in HBV-related liver injury, and the balance between host immune response and HBV replication is dynamic. The natural course of chronic HBV infection has four phases, although not all patients go through every phase.

In patients with perinatally acquired HBV infection, the first phase (immune tolerance) is characterized by the presence of HBeAg, high levels of serum HBV DNA, normal serum aminotransferases, and minimal or no inflammation on liver biopsy. During this phase, which may last 1–4 decades, spontaneous and treatment-induced HBeAg seroconversion is infrequent (<5% per year). In patients with childhood-or adult-acquired HBV infection, the “immune-tolerant” phase is short-lived or absent.

The second phase (immune-clearance/HBeAg-positive chronic hepatitis) is characterized by the presence of HBeAg, high or fluctuating serum HBV DNA levels, persistent or intermittent elevation in serum aminotransferases, and active inflammation on liver biopsy. A hallmark of this phase is flares of aminotransferases, which are believed to be manifestations of immune-mediated lysis of infected hepatocytes secondary to increased T-cell responses to hepatitis B core antigen (HBcAg) and HBeAg [2]. The duration of the “immune-clearance” phase, and the frequency and severity of the flares, correlate with the risk of cirrhosis and HCC. An important outcome of the “immune-clearance” phase is HBeAg to anti-HBe seroconversion.

The third phase is characterized by absence of HBeAg, presence of anti-HBe, relatively normal aminotransferase levels, and relatively low serum HBV DNA. Liver biopsy generally shows mild hepatitis and fibrosis, but significant

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liver injury or even cirrhosis may be observed in patients who had accrued severe liver injury during the preceding “immune-clearance” phase. This state may persist indefinitely, in which case the prognosis is generally favorable, especially if this state is reached early. However, some patients have re-activation of HBV replication either spontaneously or as a result of immunosuppression. In a study of 283 Taiwanese patients followed for a median of 8.6 years after spontaneous HBeAg seroconversion, 67% had sustained remission, 4% had HBeAg reversion, and 24% had HBeAg-negative chronic hepatitis B. Cirrhosis developed in 8% and HCC in 2% [3].

The fourth phase (re-activation of HBV replication/HBeAg-negative chronic hepatitis B) is characterized by negative HBeAg, positive anti-HBe, detectable HBV DNA, elevated aminotransferases, and continued necroinflammation [4]. Whereas most patients reach this phase after a variable duration of inactive carrier state, some progress directly from HBeAg-positive chronic hepatitis to HBeAg-negative chronic hepatitis. Patients in this phase are usually older and have more advanced liver disease, because this represents a later phase in the course of chronic HBV infection. Serum HBV DNA levels are lower than in HBeAg-positive patients but may be very high. In a study of 164 anti-HBe-positive patients who were monitored at monthly intervals for a median period of 21 months, 64% had fluctuating ALT levels, including 44% whose ALT levels were intermittently normal [5].

Spontaneous HBsAg seroclearance has been reported to occur at the rate of 0.5–1% per year in patients with chronic HBV infection [6]. HBsAg seroclearance is generally accompanied by undetectable serum HBV DNA, normalization of liver biochemistries, and improved liver histology. However, HCC may occur in a small percent of patients [7].

Importance of age of acquisition of the virus

An important aspect in the natural history of chronic hepatitis B is the timing at which an individual acquires HBV infection. Patients who acquire the infection either at birth or within the first 1–2 years of life (i.e., either “vertical” or “horizontal” transmission) typically have a prolonged immune-tolerance phase, followed by an often equally prolonged immune-clearance phase. These individuals include nearly all Asian and African patients and some from the Mediterranean countries, accounting for a majority of the world’s hepatitis B carriers [8]. About 70–85% of HBeAg seroconverters remain sustained remission and HBeAg-negative hepatitis occurs in only a quarter of HBeAg seroconverters, in whom disease progression may continue (3,9). In individuals in whom the disease

progression continues, cirrhosis can develop during the anti-HBe phase [9]. In fact, the majority (>75%) of cirrhosis complications and HCC occur after HBeAg seroconversion in this population [10]. Moreover, HBV can cause HCC even in patients who do not develop cirrhosis [11].

By contrast, patients who acquire the virus after early childhood generally do not experience the immune-tolerance phase. This group of individuals includes a majority of white patients with hepatitis B. For patients who acquire HBV infection later in life, the disease typically becomes quiescent after the immune-clearance phase, characterized by HBeAg seroconversion to anti-HBe and HBV DNA that remains at a relatively low level (i.e., <100,000 copies/ml [$\sim$ <20,000 IU/ml]) [8]. However, in Mediterranean countries HBeAg-negative chronic hepatitis B with high HBVDNA levels is frequent.

Fallacies of ALT levels for prediction of liver injury and treatment decisions

Alanine aminotransferase level is commonly used as a biochemical marker of liver disease and has been important in defining which patients are candidates for therapy. The extent of liver cell necrosis and degree of elevated ALT level do not always correlate, and ALT measurements may fail to identify patients with necro-inflammatory activity or fibrosis, as seen in hepatitis C [12, 13]. In addition, the ALT activity may vary with body mass index, sex, abnormal lipid and carbohydrate metabolism as well as the time of the day [14, 15].

Recently it has been demonstrated that ALT values above 20 IU/L are associated with increased risk of death from liver disease [15], although this study did not test HBsAg and anti-HCV. Currently recommended and revised upper limit of normal ALT values are 30 IU/L for men and 19 IU/L for women. These values are almost half of the values traditionally accepted values of the upper limit of normal ALT.

Alanine aminotransferase levels are normal in patients with immune-tolerant phase of HBV infection. Immune-tolerant patients have high viral load. Patients with e-antigen negative chronic HBV infection have fluctuating ALT levels and one point estimation of ALT may not be reliable [16]. Elevated ALT has been considered to be associated with active liver disease on histology while normal ALT with inactive histology. Many initial studies had shown that among patients with CHBV infection with normal ALT, about 50–90% of patients had either minimal changes or chronic persistent hepatitis on biopsy [17–20]. Recently, however, studies have described contrary findings also [21–24].

HBV DNA levels in patients with normal ALT

Patients who are HBeAg positive with normal ALT (immune-tolerance phase) have high levels of serum HBV DNA. Among patients who are HBeAg negative with normal ALT, it has traditionally been believed that they have low HBV DNA levels. However in a recent study, that investigated the correlation between serum ALT level and hepatitis B viral factors in HBeAg-negative patients with persistently normal serum ALT level (PNALT), it was found that 47.5% of patients with low-normal ALT (levels of less than 0.5x upper limit of normal) and 63.4% with high-normal ALT had serum HBV DNA level $>10^4$ copies/ml. Also compared with HBV carriers with low-normal ALT, those with high-normal ALT were older (41 vs. 37 years, $P < 0.001$) [21]. Another study from china showed that serum levels of HBV DNA of the patients in the immune-tolerant stage were high and 94% of them had a HBV DNA higher than 10^6 copies/ml [22].

Histology in patients with normal ALT

Elevated ALT has been considered to be associated with active liver disease on histology while normal ALT with inactive histology. Many initial studies had shown that among patients with CHBV infection with normal ALT, about 50–90% of patients had either minimal changes or chronic persistent hepatitis on biopsy [17–20]. Recently, however studies have described higher prevalence of liver injury in such patients. In a recent analysis, chronic HBV patients, increasing age, higher ALT, higher grade of inflammation on biopsy, and HBeAg positivity predicted fibrosis. In total, 18% of patients with PNALT had stage 2+ fibrosis and 34% had grade 2 or 3 inflammation. Overall 37% of patients with PNALT had significant fibrosis or inflammation [23].

Therefore, a normal ALT value does not always indicate that treatment should be withheld, as a substantial proportion of these patients do have significant liver damage. Various studies using interferon, peg interferon, Lamivudine, Adefovir have shown the importance of elevated ALT levels in predicting the response rate to therapy [24]. Thus a normal ALT value only identifies patients less likely to respond to current treatments, rather than patients who are not in need of the treatment.

HBVDNA as a prognostic marker

Measurement of serum HBV DNA is used to evaluate disease activity, assess the efficacy of antiviral therapy, and predict treatment outcomes. Studies have shown that higher HBV DNA levels are associated with increased risk of progression

to cirrhosis and HCC [10, 16, 25, 26]. Reduction in HBV DNA typically precedes other beneficial events, such as normalization of ALT levels and HBeAg seroconversion. However, HBeAg-negative patients with lower HBV DNA ($<10,000$ – $100,000$ copies/ml [~ 2000 – $20,000$ IU/ml]) may still develop significant liver disease [27].

HBV DNA levels and disease progression

Two recent reports from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus Study (REVEAL-HBV) in Asian patients clearly demonstrate the association between persistently elevated HBV DNA and the development of cirrhosis and HCC in patients infected with HBV early in life [16, 26]. This prospective cohort study included more than 3,500 HBV-infected, hepatitis C virus (HCV) antibody-negative, untreated adult participants recruited into a community-based cancer screening program in Taiwan from 1991 to 1992 who were presumed to have been infected early in life. In the first analysis, 3,653 individuals (2,925 of whom were HBeAg seronegative) were followed for a mean period of 11.4 years, representing 41,779 person-years of follow-up [26]. During this time, the cumulative incidence of HCC was 1.30% for subjects with baseline HBV DNA <300 copies/ml ($\sim <60$ IU/ml) and increased with increasing levels of HBV DNA. The direct relationship between HBV DNA and HCC was most pronounced among participants who were HBeAg-negative and had normal ALT levels and no cirrhosis at enrollment. The second analysis by this group evaluated the rates of progression to cirrhosis (diagnosed by ultrasound) in the same cohort [16]. Among 3,582 individuals (2,923 of whom were HBeAg seronegative at study entry), 365 developed cirrhosis during the 40,038 person-years of follow-up. When evaluated with respect to HBV DNA level, the cirrhosis incidence rates were 4.5% for patients with HBV DNA <300 copies/ml (~ 60 IU/ml) and 36.2% for those with HBV DNA >1 million copies/ml ($\sim 200,000$ IU/ml) at the time of enrollment ($P < .001$). This relationship was independent of both HBeAg serostatus and baseline serum ALT levels. However, 85% of the patients in the REVEAL study were HBeAg-negative and had mean age of over 40 years, therefore this group could not represent all the patients with high HBV DNA and normal ALT, particularly HBeAg-positive younger subjects whose disease progression might be more benign.

Another study also found an association between low levels of HBV DNA and chronic hepatitis B complications in Asian patients [28]. Therefore, even persistent low level viremia can cause liver damage independent from other disease factors, particularly in patients infected early in life.

Effects of long-term suppression of HBV replication on disease progression

Sustained viral inhibition can modify the natural history of CHB and prevent disease progression. Several studies show that long-term suppression of viral replication with nucleos(t)ide analogues has beneficial effects on fibrosis and cirrhosis and their complications. These studies provide support to the epidemiologic and natural history studies that have shown a relationship between persistent HBV viremia and liver disease complications in hepatitis B patients. In a study [29] evaluating the degree of HBV DNA suppression during therapy and treatment outcomes from a review of 26 clinical studies, it was found that, on-treatment suppression of viral load was a surrogate for treatment efficacy. In another study [30], after a total of 3 years of lamivudine treatment, 56% of patients showed at least a 2-point improvement in histologic activity index scores, bridging fibrosis improved by at least 1 point in 63% and cirrhosis improved in 73% (score reduced from 4 to 3 or lower). Similar improvements in histology have been shown for adefovir [31] and entecavir [32, 33] treatment also. These studies demonstrate that fibrosis, and even cirrhosis, are partially reversible with long-term nucleos(t)ide treatment that suppresses HBV DNA to low or undetectable levels.

Effect of treatment on progression to cirrhosis complications and HCC

Studies have investigated the effects of antiviral agents on the development of cirrhosis complications and HCC. In one study, 651 patients (98% Asian; 58% HBeAg positive) with histologically confirmed advanced fibrosis or cirrhosis were randomly assigned to receive either lamivudine ($n = 436$) or placebo ($n = 215$) for up to 5 years [34]. After a median treatment duration of 32.4 months, the study was terminated because significantly fewer patients receiving lamivudine died of liver-related causes or developed cirrhosis complications (including hepatic decompensation, spontaneous bacterial peritonitis, and bleeding esophageal varices) or HCC compared with the placebo arm (7.8% vs. 17.7%, respectively; $P = .001$). Another study, involving long-term follow-up of 266 asymptomatic, noncirrhotic HBeAg-positive Chinese patients treated with lamivudine or placebo, showed that prolonged suppression of HBV DNA with antiviral therapy reduces the risk of chronic hepatitis B complications in asymptomatic patients as well as those with pre-existing advanced fibrosis or cirrhosis. [35].

Studies also suggest that long-term suppressive antiviral therapy may have some effect on HBV covalently closed circular (ccc) DNA. This HBV cccDNA in liver cells is the

probable source of viral rebound after treatment is discontinued. However, it has been postulated that with prolonged suppressive therapy, cccDNA may become depleted through natural cell division and cell death [36]. Studies with each of the available nucleos(t)ide therapies—lamivudine[37], adefovir[38], and entecavir[39] and combination treatment with pegylated interferon alpha-2b and adefovir dipivoxil [40] have supported this concept.

However, long-term treatment with antivirals can lead to drug resistance, which can lead to hepatitis flare resulting in losing the clinical benefit and this can lead to fatal complications particularly in those with cirrhosis.

Cost-effectiveness of treatment of immune-tolerant patients

In a cost-effectiveness analysis, to assess whether immune-tolerant patients with high HBV DNA levels should undergo treatment, a lifetime Markov model was created to evaluate the cost-effectiveness of two strategies namely HBV DNA suppression with lamivudine, or no treatment, for immune-tolerant hepatitis B. Compared with the no treatment strategy, lamivudine therapy was more expensive but more cost-effective with an additional cost of \$5,784 and \$12 584 per quality adjusted life year gained in males and females, respectively. Treatment resulted in a gain in life expectancy and a decrease in lifetime risk of HCC and cirrhosis [41]. However, analysis in this study has several limitations. The data on disease progression in this study was based on the data from REVEAL study mainly representing the middle-aged patients with HBeAg-negative CHB and hence they were not the true immunotolerant patients (HBeAg-positive, high HBV DNA, and normal ALT). The younger patients with HBeAg-positive, high HBV DNA, and persistent normal ALT have much more benign course of disease progression. Also, this study does not represent the real practice as they did not add or shift therapy when drug resistance emerges. The risk of very long-term therapy in patients with high viral load and normal ALT was not properly included, as it is known that normal ALT and high HBV DNA at baseline are predictors of poor response to Lamivudine therapy. Therefore, the additional cost may not be cost-effective especially in Asia, where economic constrain is an important factor.

In summary, a fair proportion of patients with CHB infection with normal ALT have high HBV DNA levels and liver damage. They should be considered for treatment based on the HBV DNA levels assessed by sensitive real time PCR and histological activity and the treatment should be individualized.

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