Expanding antiviral therapy indications for HBeAg-negative chronic hepatitis B patients with normal ALT and positive HBV DNA

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Abstract

With the improved efficacy and accessibility of antiviral agents as well as the concerns about disease progression, there is a hot discussion on whether HBeAg-negative chronic hepatitis B (CHB) patients with normal alanine aminotransferase (ALT) and positive HBV DNA should be treated. According to the international guidelines on the stages of the natural history of HBV infection, HBeAg-negative CHB patients with normal ALT and positive HBV DNA can be divided into two groups: one is the well-known "inactive carrier phase", which is defined as serum HBV DNA < 2000 IU/ml and no significant liver inflammation; and the other is the "indeterminate phase", which is defined as serum HBV DNA ≥ 2000 IU/ml regardless of the pathological changes in liver tissue, or HBV DNA < 2000 IU/ml but accompanied by significant pathological changes in the liver. In this minireview, we will expound the disease characteristics, disease progression, and clinical management status of these two groups. Based on the analysis, we propose that HBeAg-negative patients with normal ALT but detectable serum HBV DNA should be treated, regardless of their age, family history of hepatocellular carcinoma (HCC) or the severity of liver necroinflammation. Expanding the indications of antiviral therapy will help improve the survival and quality of life of patients by preventing disease progression, and consequently reduce the risk of HCC development.

Keywords: chronic hepatitis B, negative HBeAg, normal ALT, inactive carrier, positive HBV DNA, indeterminate phase

Introduction

Chronic hepatitis B virus (HBV) infection continues to be a substantial public health burden estimated to impact nearly 300 million persons worldwide, accounting for 30% of all deaths from cirrhosis and 40% of all deaths related to hepatocellular carcinoma (HCC) globally.1 Identifying people at high risk of disease progression and initiating treatment in time is the most effective measure to reduce complications associated with chronic HBV infection.

Serum alanine aminotransferase (ALT) is a sensitive and commonly used indicator of hepatocellular injury, with normal ALT generally considered as absence of active inflammation in the liver. But studies have shown that a high proportion of HBeAg-negative patients with normal ALT still have significant hepatic necroinflammatory activity and remain at risk of disease progression to cirrhosis and HCC development. Sustained positive HBV DNA implies persistent replication of HBV, which can stimulate host immune responses, leading to hepatocyte destruction and regeneration, accompanied by the development of fibrosis and eventually cirrhosis.2 In addition, HBV DNA can integrate into the human genome inducing HCC, through insertional mutagenesis, alteration of gene expression, and chromosomal instability.3 Several studies have also confirmed the dose-dependent relationship between serum HBV DNA levels and the incidence of cirrhosis, HCC, and related death.2,4 Even patients with lower level HBV DNA (<2000 IU/ml) are still at risk for disease progression, especially the development of HCC.5,6

At present, there is no consensus on the necessity of antiviral therapy in HBeAg-negative patients with normal ALT and positive HBV DNA (Table 1). Reasons opposing treatment include the poor patient compliance, risk of viral resistance arising from long-term treatment, and benign prognosis without treatment in some patients, especially for inactive carriers. However, there are emerging viewpoints supporting treatment to such patients. Serum ALT levels cannot accurately predict disease progression but serum HBV DNA levels are linearly associated with HCC risk in HBeAg-negative patients.6 Currently, first-line antiviral drugs have a high virological response rate and low drug resistance rate. The significantly decreased treatment costs with medical insurance reimbursement have also increased its accessibility to patients at this stage. From the perspective of primary prevention, initiating viral therapy before progressing to cirrhosis and HCC, is cost-effective.7

HBeAg-negative CHB patients with normal ALT and positive HBV DNA are classified as the "inactive carriers" phase and the "indeterminate" phase.8 In this minireview, we analyze the disease characteristics, disease progression, and treatment status of the two groups, discuss the necessity of expanding antiviral treatment indications, and propose clinical management recommendations for the sub-population of CHB patients.

Accurate understanding of the natural history of HBeAg-negative CHB patients with normal ALT and positive HBV DNA

Chronic HBV infection is a dynamic process reflecting the interaction between HBV replication and the host immune response.9
Table 1. Pros and cons on the antiviral therapy for HBeAg-negative CHB patients with persistently normal ALT but positive HBV DNA.

Views of supporting antiviral therapy

- Cirrhosis progression, HCC development, and inflammatory reactivity are potential risks.
- Peg-IFN-α monotherapy combined with NAs regimen can significantly improve clinical cure rates in some advantageous patients.
- Current clinical first-line NAs drugs have high accessibility, reduced treatment costs, high efficiency and low drug resistance, and low incidence of side effects.
- Effective patient education will improve adherence.
- Some patients willingly request treatment to reduce the impact of HBV infection on life and work.

Views of opposing antiviral therapy

- The prognosis is good with the rare occurrence of cirrhosis or HCC if patients remain in the inactive CHB infection phase.
- Antiviral drugs cannot eradicate cccDNA, and long-term maintenance therapy is required.
- Long-term treatment leads to a high incidence of adverse drug reactions and poor patient compliance, and increases the risk of viral resistance and fulminant hepatic failure after drug withdrawal.
- Some patients may lose HBsAg spontaneously.
- The clinical benefit of antiviral therapy is unknown.

Abbreviation: CHB, chronic hepatitis B; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; NAs, nucleos(t)ide analogs; Peg-IFN-α, peginterferon alfa; cccDNA, covalently closed circular DNA.

Figure 1. Classification of HBeAg-negative chronic HBV-infected patients with normal ALT and positive HBV DNA. ULN, upper limits of normal; G2/S2, grading 2/staging 2, indicating the presence of significant inflammation/fibrosis in the liver.

Taking into account the presence of HBeAg, HBV DNA levels, ALT values, and eventually the presence or absence of liver inflammation, the natural history of chronic HBV infection can be classified into four phases: Immune-tolerant phase, HBeAg-positive immune-active phase, inactive chronic hepatitis B phase (also termed ‘inactive carrier’ phase), and HBeAg-negative immune reactivation phase. Generally, patients in different phases of natural history have different prognoses and management.

Accordingly, HBeAg-negative CHB patients with normal ALT and positive HBV DNA can be in one of the following two phases: the well-defined inactive carrier phase, and the “indeterminate” phase that cannot be classified into any of the known phases (Fig. 1).

**Diagnosis of the inactive carrier phase should be cautious**

The inactive carriers phase is characterized by negative HBeAg, positive anti-HBe, normal ALT, and undetectable or low HBV DNA levels (<2000 IU/mL). Besides, liver biopsy shows no significant pathological changes in the liver, which is an essential criterion for the diagnosis of the real “inactive carrier”. Indeed, patients with low quantitative HBsAg (<1000 IU/mL) and undetectable HBV DNA are more likely to be real “inactive carriers”.

The diagnosis of inactive carrier tends to be tricky and therefore should be cautious, if there is no liver biopsy result. Studies with liver biopsy revealed the existence of significant inflammation in a considerable proportion HBeAg-negative CHB patients with...
normal ALT and serum HBV DNA < 2000 IU/mL. Although serum ALT is a sensitive indicator reflecting liver injury, normal ALT does not exclude the absence of significant inflammation in the liver and does not predict the risk of long-term disease progression. Moreover, the upper limit of normal ALT differs by region, and a higher normal upper limit of ALT may reduce the diagnostic accuracy of liver inflammatory activity. Some alternative non-invasive methods to estimate the degree of liver fibrosis have been introduced in clinical practice, including FibroTest and vibration-controlled transient elastography (VCTE). But these tests are better at excluding confirmed advanced fibrosis or cirrhosis than identifying emerging fibrosis, which is not conducive to early initiation of treatment. Additionally, the diagnostic accuracy can be influenced by various factors, such as hepatic necroinflammation, elevated serum total bilirubin levels, hepatic steatosis, obesity, congestive heart failure, alcohol intake, and the experience of the operators of VCTE.

**Patients in the indeterminate phase are not rare**

“Indeterminate phase” is not specific to the disease of CHB but a term that reflects patients’ current disease status beyond conventionally defined boundaries. There is no uniform definition for the “indeterminate phase” of chronic HBV infection. At present, the indeterminate phase refers to CHB patients whose serum HBV DNA, ALT levels, and the severity of liver histopathology do not fit into well-described phases of natural history of chronic HBV infection, as pointed out in the hepatitis B guidelines of American and European Associations for the Study of Liver Diseases. For example, in the group of HBeAg-negative (HBeAb-positive) patients with normal ALT, those with high HBV DNA levels (≥2000 IU/mL), or those with a low level of HBV DNA (<2000 IU/mL) but with significant liver inflammation or fibrosis (≥G2/S2) can all be classified in the indeterminate phase (Fig. 1). According to the published literature, about 30%–40% of patients may fall into this stage, and most are HBeAg-negative. In a retrospective study by Yao et al., 24.73% (327/1322) of HBeAg-negative patients with normal ALT levels and serum HBV DNA ≥ 2000 IU/mL were classified into the indeterminate phase based on the 2018-AASLD criteria.

Some scholars have proposed that the indeterminate phase may be a transitional state of the natural history of HBV infection. Because chronic HBV infection is a dynamically changing and continuously evolving process, which is artificially divided into four distinct stages, with no obvious boundary between any two adjacent phases. A multicenter, retrospective cohort study found, by up to 5 years of follow-up, 79.3% (963/1303) of indeterminate patients at baseline remained indeterminate, 10.7% (139/1303) transitioned to the immune active phase, 14.3% (186/1303) transitioned to the inactive phase, and 1.2% (15/1303) transitioned to the immune tolerant phase. In addition, the levels of ALT and HBV DNA can be affected by the host, viral factors, and other exogenous factors, such as alcohol consumption, drugs, other viral infections, fatty liver disease, etc., resulting in atypical clinical manifestations and the uncertainty of immune stage.

**Suggestions for management of the two phases by existing guidelines**

For patients in the inactive carrier phase, antiviral therapy is not recommended by current international guidelines. Previous studies revealed that, if they remain in this immune status, patients have a low risk of developing cirrhosis or HCC and have an annual probability of 1%–3% of spontaneous HBeAg loss. However, most of these studies on the clinical outcomes enrolled relatively young patients, and the follow-up periods were not long enough (most around five years). Therefore, the long-term prognosis of inactive carrier is still inconclusive. It is unclear whether the favorable outcomes observed can be extrapolated to older inactive carriers identified in different clinical settings.

Additionally, it is not a truly ‘inactive’ disease phase, since the risk of spontaneous reactivation (20%–30% of individuals) and the potential risk of cirrhosis and HCC development are not negligible. Prolonged low-level viremia in these patients will induce insidious and continual liver damage, leading to a higher risk of HCC and liver-related death compared with individuals without HBV infection.

Therefore, the premises of no treatment depend on accurate diagnosis and patient compliance with regular examinations. Because of the long-term concept of regular follow-up rather than treatment, the lack of data on the clinical outcomes of antiviral therapy in inactive carriers makes the recommendation for immediate treatment insufficient.

For patients in the indeterminate phase, the major guidelines do not provide recommendations, and the necessity of initiating treatment remains controversial. A retrospective clinical study on 150 HBeAg-negative patients with normal ALT and HBV DNA ≤ 20 000 IU/mL found that the vast majority of patients had an excellent clinical prognosis after a median follow-up of 8.2 (5–19) years, with rare occurrences of active hepatitis, and beneficial events, such as loss of HBsAg or conversion to an inactive carrier state, often occurred. This was consistent with the findings of Oliveri et al. in 46 HBeAg-negative patients with normal ALT and low viral replication (HBV DNA ≤ 20 000 IU/mL) who were followed up for 57.2 (8.5–158.3) months. Therefore, they proposed that it was safe to avoid antiviral therapy but still need long-term follow-up to monitor disease progression. However, Daniel et al. found that, without treatment, the indeterminate phase had a 14 times higher risk of HCC development than the inactive phase. The total indeterminate patient cohort at baseline and the indeterminate patients remaining throughout the follow-up had a higher 10-year cumulative incidence of cirrhosis than the inactive patients. Similarly, an observational study with a median of 8.9 years of follow-up in 5414 patients, showed that the untreated HBeAg-negative CHB patients with high HBV DNA levels (≥2000 IU/mL) and persistently normal ALT levels (replicative phase) had a significantly higher risk of HCC and death/transplantation, than those in the active phase (ALT ≥ 2ULN) treated with oral antiviral agents.

Based on these studies, some scholars have proposed that treatment should be initiated as early as possible to reduce the risk of disease progression as long as HBV DNA is detectable, whether HBeAg is negative or not. Some scholars have suggested that dynamical evaluation for this immune stage should be the first. For those whose immune stage remains undefined, the severity of liver lesions and the risk of disease progression should be comprehensively evaluated to determine whether treatment is needed instead of sticking to the ALT level and immune stage. Others supported aggressive antiviral therapy for patients with a high risk of disease progression. Meanwhile, studies are desperately needed to fill up the knowledge gap on the benefit of antiviral treatment for such patients.

**The necessity and advantages of expanding antiviral therapy indications**

Liver biopsy found moderate or severe liver necroinflammation and/or fibrosis in some HBeAg-negative CHB patients, although...
with normal ALT. For patients in this phase, serum HBV DNA load is an independent risk factor for disease progression, with high-level HBV DNA (>2000 IU/mL) being strongly associated with both HCC and cirrhosis. Moreover, patients with lower level HBV viremia (<2000 IU/mL) are still at risk for disease progression, especially the development of HCC.

However, presently, there are still many undiagnosed and untreated CHB patients worldwide. Though many patients hope to get treated to reduce the negative impact of HBV infection on life and work, the existing guidelines discourage physicians to administer treatment to them. With the large sub-population excluded from present treatment indications recommended by guidelines, it will be difficult to achieve the ambitious goal set by WHO in 2016: to eliminate the global harm of viral hepatitis by 2030.

The guidelines do not cover all high-risk groups. Traditional treatment indications are generally provided to individuals at high risk of disease progression, namely those with elevated ALT levels, active viral replication, and advanced fibrosis or cirrhosis. But some patients out of the treatment indications suffer from liver-related disease progression. In addition, some recommendations are based on experts’ experience and lack of clinical data. Therefore, the advice of guidelines needs to be taken dialectically.

It is widely accepted that antiviral therapy can improve survival and reduce the complications of liver disease. Compared with HBeAg-positive patients, HBeAg-negative patients have a higher virological response rate to antiviral therapy and a higher chance of achieving clinical cure through treatment. Previously, treatment was limited for the high rate of drug resistance and drug side effects, such as lamivudine (LAM) and adefovir dipivoxil (ADV), the concerns about poor compliance due to long-term treatment and high costs, and the uncertainty of clinical benefits of antiviral therapy. Currently, the clinical first-line drugs, such as entecavir (ETV) and tenofovir alafenamide (TAF), are highly effective with low-resistance, have a low incidence of drug side effects, and can be reimbursed by medical insurance.

**Recommendations on the management of HBeAg-negative patients with normal ALT**

For patients with HBV DNA ≥ 2000 IU/mL, antiviral therapy should be initiated without hesitation. For patients with HBV DNA < 2000 IU/mL, decision depends on the HBV DNA load: antiviral therapy should be initiated without hesitation when the HBV DNA load is detectable by high-sensitivity HBV DNA quantitative detection; if HBV DNA is undetectable by high-sensitivity HBV-DNA quantitative detection, with false negative results excluded, liver biopsy is recommended. Antiviral therapy should be considered in the presence of moderate or severe inflammation and/or significant fibrosis (≥G2/F2) in the liver; and if not (<G2/F2), regular follow-up should be recommended (Fig. 2).
Notably, reasons for antiviral therapy in patients with undetectable HBV DNA but with significant liver disease (≥G2/F2) are as follows: On the one hand, the “undetectable” result of high-sensitivity HBV-DNA quantitative test can provide information that the HBV DNA load in the tested sample is below the lower detectable limit of the instrument, but does not mean negative amplification of HBV DNA in the serum. Ruling out other factors contributing to liver damage, the significant liver disease could be attributed to chronic HBV infection, because the covalently closed circular DNA (cccDNA) still presents in the hepatocytes reflected by the positive HBsAg, so these patients remain at risk of disease recurrence and progression. Also, other indicators may be considered to assess the necessity of treatment, such as serum HBV pregenomic RNA (pgRNA), a clinical marker for cccDNA activity. On the other hand, study has confirmed that clinical cure by treatment will further reduce the risk of developing cirrhosis and HCC. Still the clinical benefits of antiviral therapy in this population need to be confirmed in the future.

Conclusions
The improved efficacy of antiviral drugs and the reduced treatment costs provide a fundamental basis for expanding the indications for antiviral therapy. Whether in the inactive carrier or indeterminate phase, patients with positive HBV DNA are at risk of disease progression. Thus, HBeAg-negative CHB patients with normal ALT and positive HBV DNA should be treated, regardless of age, family history of liver cancer, or histologic disease severity. This is a preventive treatment measure that simplifies the management of chronic HBV infection, reduces the risk of missed treatment for potentially high-risk groups due to normal ALT, and makes us closer to the goal of eliminating the global harm of viral hepatitis by 2030.

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Author contributions
JZ and EC: Proposed the ideas, designed and wrote the manuscript. FW and LL: Searched literature and assisted in conducting the manuscript revision.

Conflict of interest
The authors declare that they have no competing interests.

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