



## Review

# Management of chronic hepatitis B patients in immune-tolerant phase: what latest guidelines recommend

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The natural history of chronic hepatitis B (CHB) is complex and may run through different immune phases that may overlap. In particular, the immune-tolerant phase is the most interesting and not as well understood as we thought. The concept of true immune tolerance have been under challenged from immunology points of view. The major international guidelines have not yet reached a consensus on the definition of the immune-tolerant phase. While positive hepatitis B e antigen (HBeAg), high serum hepatitis B virus (HBV) DNA and normal serum alanine aminotransferase (ALT) levels are the three key features of this phase, some guidelines also put age into consideration. A new nomenclature, Phase 1 or HBeAg-positive chronic HBV infection, is given by the latest European Association for the Study of the Liver (EASL) published in April 2017. While current guidelines advise against starting antiviral treatment for immune-tolerant CHB patients, some new data suggest treating such patients may reduce the risk of liver fibrosis progression and hepatocellular carcinoma. ([Clin Mol Hepatol 2018;24:108-113](#))

**Keywords:** Chronic hepatitis B; Hepatocellular carcinoma; Immune tolerance; Liver fibrosis; Positive HBeAg

## INTRODUCTION

Chronic hepatitis B (CHB) is a life-threatening liver disease affecting 257 million people worldwide, in particular in the Asia-Pacific regions where the infection is endemic.<sup>1</sup> The natural history of CHB, in particular in patients infected via vertical transmission, is complex and may run through different immune phases that may overlap. Conventionally, the most commonly described four phases of CHB include immune-tolerant phase, immune clearance or active phase, inactive carrier phase and reactivation phase.<sup>2</sup> Among these four phases, immune-tolerant phase is not as well understood and the concept of true immune tolerance have been

under challenged. In this review, the latest knowledge on the definition, natural history and management recommended by latest international practice guidelines for patients in the immune-tolerant phase will be concisely discussed.

## DEFINITION OF IMMUNE-TOLERANT PHASE

The major international guidelines have not yet reached a consensus on the definition of immune-tolerant phase. The latest guidelines published in 2016 by the American Association for the Study of Liver Diseases (AASLD) define immune-tolerant phase in

### Abbreviations:

ALT, alanine aminotransferase; CHB, Chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MTCT, maternal-to-child transmission; TDF, tenofovir disoproxil fumarate; AASLD, the American Association for the Study of Liver Diseases; APASL, the Asian Pacific Association for the Study of the Liver; EASL, the European Association for the Study of the Liver; ULN, upper limit of normal; WHO, World Health Organization

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a more traditional way, *i.e.* normal alanine aminotransferase (ALT; <30 U/L in men and <19 U/L in women as upper limit of normal [ULN] rather than local laboratory reference ranges), elevated hepatitis B virus (HBV) DNA (typically above 1 million IU/mL), positive hepatitis B e antigen (HBeAg), and minimal inflammation and fibrosis shown in liver histology.<sup>3</sup> This is in contrast to another HBeAg-positive situation, the immune-active phase, with the key distinguish features of elevated serum ALT, high but perhaps not as high serum HBV DNA (>200,000 IU/mL) and moderate-to-severe inflammation or fibrosis shown in liver histology.<sup>3</sup> On the other hand, the 2015 update of the practice guidelines of the Asian Pacific Association for the Study of the Liver (APASL) define immune-tolerant phase slightly differently from AASLD, mainly a different threshold of serum HBV DNA (>20,000 IU/mL), and putting up age as one of the criteria (typically below 30 years old).<sup>4</sup>

The concept of true immune tolerance have been challenged, as immunological studies revealed children and young adults with CHB have an immune profile that is less compromised than that observed in older patients.<sup>5</sup> With these new observations, the newest international guidelines at the time of writing, the European Association for the Study of the Liver (EASL) practice guidelines published in April 2017, give this phase a new nomenclature – Phase 1 or HBeAg-positive chronic HBV infection – instead of the conventional immune-tolerant phase.<sup>6</sup> The characteristics of this phase include what the AASLD guidelines describe, together with a few special features at the molecular and immunological levels namely high level of HBV DNA integration and clonal hepatocyte expansion,<sup>7</sup> possible proceeding hepatocarcinogenesis, preserved HBV specific T cell function at least until young adulthood, very low rate of spontaneous HBeAg loss and highly contagious due to the high levels of HBV DNA.<sup>6</sup>

## NATURAL HISTORY OF CHB PATIENTS IN IMMUNE-TOLERANT PHASE

### From immune-tolerance to HBeAg seroclearance / seroconversion

An important Korean study recruited 133 children (mean age 10.6 years) with immune-tolerant CHB over more than 10 years reported that a low rate (1.7/100 patient-years) of conversion to early immune clearance phase. The estimated transition rate from immune tolerance to clearance increased dramatically with age: it was 4.6%, 7.1%, and 28.0% for patients aged 6, 6-12, >12 years,

respectively.<sup>8</sup> Another Korean study of 90 adult HBeAg CHB patients revealed spontaneous HBeAg seroconversion in patients with HBeAg-positive CHB was rare (1/90; 1.6%) within 6 months; in contrast biochemical deterioration occurred up to 18.9%.<sup>9</sup> But this may be different from other parts of the world as Korea is one of the endemic areas of genotype C HBV infection, which is well-known to be associated with delayed HBeAg seroconversion.<sup>10,11</sup> In a study of 240 Taiwanese CHB patients (of genotype B and C HBV) who were HBeAg positive and normal ALT at baseline, 85% patients had spontaneous HBeAg seroconversion at age 15 to 39 years.<sup>12</sup>

### Liver fibrosis progression

The Taiwanese study described previously showed a small yet non-negligible risk of progression from immune-tolerant phase liver cirrhosis, which occurred in 13 patients (5.4%) after a median follow-up of 10.5 years.<sup>12</sup> The key risk factors included older age of HBeAg seroconversion and hepatitis relapse associated.<sup>12</sup> A small retrospective histological series of 40 immune-tolerant CHB patients showed 50% of them had no fibrosis at all; while the other 50% had only F1 fibrosis.<sup>13</sup> This implies liver fibrosis progression is uncommon in immune-tolerant CHB patients.

Subsequently another Hong Kong study involved 453 Chinese HBeAg-positive patients revealed that age >35 years and high-normal ALT>0.5xULN predicted advanced liver fibrosis defined by liver stiffness measurement (LSM) by transient elastography.<sup>14,15</sup> Nonetheless this so-called “high-normal” ALT would be defined as abnormal according to the current AASLD criteria and hence those patients were not truly of immune tolerance. Yet in patients with ALT≤0.5xULN, 6.8% still had advanced fibrosis, the probability would be even high in the subgroup of patients above 35 years old (15%). As LSM is least affected if serum ALT is normal,<sup>16,17</sup> these observations supported what the latest EASL guidelines point out not all patients in the immune-tolerant phase would have minimal fibrosis.<sup>6</sup>

Histology series in Asian-Americans with positive HBeAg, normal ALT (AASLD criteria) and high HBV DNA (mean 7.7 logs copies/mL) demonstrated up to one-quarter of patients had significant fibrosis of F2-3.<sup>18</sup> A prospective cohort involved paired transient elastography examinations at a 3-year interval, liver fibrosis progression happened in 3.1% among immune-tolerant patients. Liver fibrosis progressed at similar rate (3.3%) if the immune-active patients received antiviral treatment, but higher risk of such patients did not receive antiviral treatment (13.3%).<sup>19</sup>

## Hepatocellular carcinoma

HBeAg positivity has known to be a risk factor of hepatocellular carcinoma (HCC).<sup>20</sup> HCC incidence was 1,169, 324 and 39 per 100,000 person-years among subjects who were positive for both hepatitis B surface antigen (HBsAg) and HBeAg, positive for HBsAg only, and negative for both, respectively.<sup>20</sup> However, HBeAg positivity was not equal to immune tolerance as serum ALT was not analyzed; the information of any subsequent immune clearance or HBeAg seroconversion was also not provided. Subsequently a few HCC risk scores also include HBeAg positivity as one of the factors contributing to the scores. For example, REACH-B score identified gender, age, serum ALT level, HBeAg status, and serum HBV DNA level as the factors increasing the HCC risk in non-cirrhotic CHB patients.<sup>21</sup> But similar to that landmark study, this HBeAg positivity does not necessarily reflecting immune tolerance; instead it reflects immune clearance as patients with elevated ALT and older age are two other risk factors of HCC. Other common HCC risk scores namely CU-HCC score,<sup>22,23</sup> GAG-HCC score<sup>24</sup> and LSM-HCC score<sup>25</sup> do not include HBeAg positivity as a contributing factor, instead they put much more weight and emphasis to the presence of cirrhosis or high LSM. This also indirectly reflect patients in immune-tolerant phase are not at increased risk of HCC.

More direct evidence had not been available until very recently proving the above concept could have been wrong. A Korean historical cohort study of 413 HBeAg-positive CHB patients with normal ALT (AASLD criteria), high HBV DNA levels ( $\geq 20,000$  IU/mL) and no evidence of cirrhosis were compared another cohort of 1,497 CHB patients in immune-clearance phase treated with NA.<sup>26</sup> During the long-term follow up, the 10-year estimated cumulative incidences of HCC was significantly higher in the untreated immune-tolerant patients than the treated patients in immune-clearance phase (12.7% vs. 6.1%;  $P=0.001$ ).<sup>26</sup> This observation with different conclusion from the above studies may imply either these initially immune-tolerant patients had evolved over time; or the NA treatment reduced the risk of HCC so much that the risk would be even lower than untreated immune-tolerant patients.

## TO TREAT OR NOT TO TREAT?

### Virologic response of antiviral treatment for immune-tolerant patients

A multicenter clinical trial comparing TDF versus TDF and em-

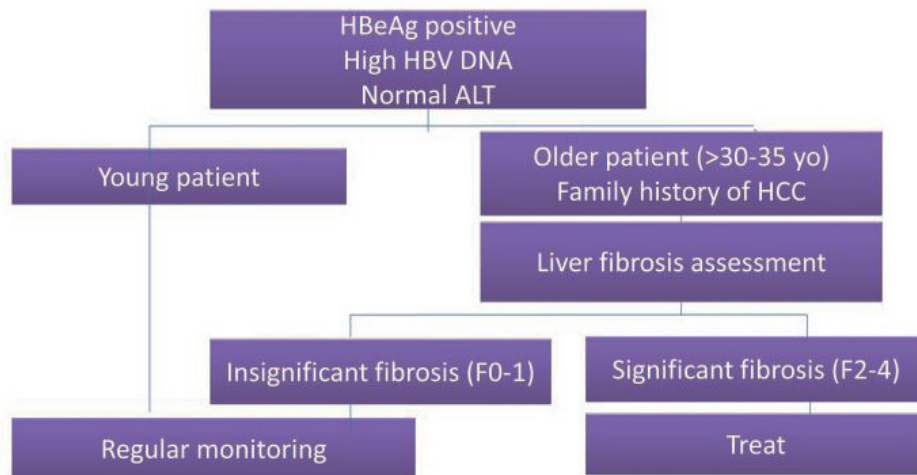
tricitabine combination therapy for four years in 162 patients with immune-tolerant CHB revealed low virologic response rates – 0% to 5% of HBeAg seroconversion, and 0% HBsAg seroclearance.<sup>27</sup> A extension follow-up study for another 4 years of a subgroup of 20 Chinese patients from this trial showed a high rate of virologic and clinical relapse after stopping NA in these immune-tolerant patients.<sup>28</sup> All patients had virologic relapse (HBV DNA  $>2,000$  IU/mL) at week 4, 10 (50%) patients had clinical relapse (HBV DNA  $>2,000$  IU/mL and ALT  $>2$ xULN); among the 9 untreated patients, 7 remained immune tolerant and 2 had HBeAg seroconversion subsequently.<sup>28</sup> These observations imply treating patients with immune-tolerant CHB did not alter its natural history much; once the antiviral treatment is stopped, it would be back to square one of high serum HBV DNA.

### Recommendations from international guidelines

Because of the above observations from the landmark clinical trial, the latest AASLD guidelines recommend against antiviral therapy for adults with immune-tolerant CHB.<sup>3</sup> The rationale behind is mainly the lack of studies demonstrating antiviral is beneficial in reducing rates of HCC, cirrhosis and liver-related death in patients with immune-tolerant CHB; hence potential harm, including cost, antiviral drug side effects and development of resistance, outweighs its benefits.<sup>3</sup> AASLD suggests that ALT levels be tested at least every 6 months for adults with immune-tolerant CHB to monitor for potential transition to immune-active or -inactive CHB.<sup>3</sup>

EASL guidelines have a slightly different view on that; delayed HBeAg seroconversion beyond 30 years old is already a treatment indication, as patients with HBeAg-positive chronic HBV infection (i.e. persistently normal ALT and high HBV DNA levels) may consider treatment if they are older than 30 years regardless of the severity of liver histological lesions.<sup>6</sup> In contrast, such patients younger than 30 years and do not fulfill any of the treatment indications otherwise should be followed at least every 3–6 months.

Antiviral treatment is recommended when HBeAg-positive patients are already out of immune-tolerant phase, namely with high serum ALT  $>2$ x ULN and HBV DNA  $>20,000$  IU/mL, or serum ALT  $>1-2$ x ULN and HBV DNA  $>2,000$  IU/mL with moderate/severe inflammation or significant liver fibrosis. Certainly, HBeAg-positive patients with compensated liver cirrhosis with detectable HBV DNA (while APASL guidelines set HBV DNA  $>2,000$  IU/mL or elevated ALT with detectable HBV DNA), or decompensated liver cirrhosis with detectable HBV DNA.<sup>3,4,6</sup>



**Figure 1.** Importance of assessment of liver fibrosis in HBeAg-positive patients.

Apart from the conventional serum ALT and HBV DNA levels, EASL guidelines also put the following factors into consideration before starting antiviral treatment for patients at this phase – HCC risk, reactivation and transmission of HBV; and extrahepatic manifestation.<sup>6</sup>

### Importance of assessment of liver fibrosis in HBeAg-positive patients (Fig. 1)

When we are uncertain if an HBeAg-positive patient is really still of immune tolerance, liver biopsy considered to detect advanced liver fibrosis for antiviral therapy, or alternatively with non-invasive assessments such as transient elastography and/or serum tests as first screening tool.<sup>29-32</sup> APASL guidelines 2015 recommend that noninvasive methods for the estimation of the extent of fibrosis are useful in selecting patients for liver biopsy. Patients with the suggestion of significant fibrosis by noninvasive markers (mean liver stiffness >8 kPa (by Fibroscan) or aspartate aminotransferase (AST)-to-platelet ratio index (APRI) >1.5) should be considered for liver biopsy.<sup>4</sup>

World Health Organization (WHO) issued her very first specific guidelines for the prevention, care and treatment of persons with CHB in March 2015.<sup>33</sup> With a global view and coverage (with Africa also included), WHO guidelines provide very practical recommendations with special consideration in resource-limited settings. For example, APRI is recommended as the preferred non-invasive test to assess for the presence of cirrhosis at a cutoff of 2 for adult patients in resource-limited settings.<sup>33</sup> Other more advanced non-invasive tests namely transient elastography or FibroTest may be preferred in settings that are more resourceful.<sup>33</sup>

### Special consideration - Prevention of Maternal-to-Child Transmission of HBV

One of the recent breakthrough in CHB is the risk and prevention of maternal-to-child transmission (MTCT) of HBV. Multiple observational studies establish the risk of MTCT of HBV in HBeAg-positive mothers despite HBV vaccination to infants, as very often they have very high serum viral load (6 to 9 log<sub>10</sub> IU/mL).<sup>34,35</sup> This led to the subsequent prospective study of 118 Taiwan HBeAg-positive pregnant women with serum HBV DNA  $\geq 7.5$  log<sub>10</sub> IU/mL.<sup>36</sup> This was the first study to prove that antiviral treatment with TDF at third trimester to one month post-partum reduce the HBsAg positivity rate of infant compared to no antiviral treatment versus no medication (1.54% vs. 10.71%;  $P=0.048$ ). A multicenter randomized placebo-controlled trial in China provided the level I evidence of the prevention of MTCT of HBV with antiviral treatment at third trimester.<sup>37</sup> With a slightly lower maternal serum HBV DNA (<200,000 IU/mL) as the inclusion criterion, the per-protocol analysis of the primary outcome, infants with serum HBV DNA >20 IU/mL or HBsAg positivity at 28 weeks of age was 0% in the TDF arm and 6.82% in the placebo arm.<sup>37</sup>

With these new data from two important studies, the latest international guidelines recommend HBeAg-positive mothers with HBV DNA >10<sup>6</sup> IU/mL<sup>6</sup> or 200,000 IU/mL<sup>3</sup> should receive oral antiviral treatment during the last trimester, together with hepatitis B immunoglobulin (HBIG) and HBV vaccination for the newborn. The area of uncertainty now leaves when to stop antiviral treatment. The guidelines recommend to stop immediately or up to 3 months post-partum if the mothers do not meet treatment criteria otherwise.<sup>3,6</sup> Nonetheless it would be important to closely moni-

for the mother as virologic relapse is a rule rather than exception; biochemical flare also occurs but luckily no hepatic decompensation has been observed.<sup>36,37</sup>

## HCC RISK AFTER ANTIVIRAL TREATMENT

Existing literature on HCC risk in immune-tolerant CHB is scarce. A recent Korean nationwide real-life study of 484 HBeAg-positive CHB patients with normal ALT (<40 U/L), high HBV DNA (>20,000 IU/mL) and no cirrhosis shed some light on this important yet difficult-to-study topic. Eight-seven of 484 patients received NA; compared to the 397 untreated patients in the control group, NA treatment significantly reduced risk of HCC (with an adjusted hazard ratio of 0.189,  $P=0.004$ ).<sup>38</sup> Even though we cannot exclude some of these HBeAg-positive CHB patients might be in the early HBeAg seroclearance phase (as the ALT cutoff was higher than what international guidelines recommend), this important observation, in-line with studies involved patients in other phases of CHB,<sup>39</sup> that NA treatment reduces risk of HCC.

## CONCLUSION

For HBeAg positive patients with normal ALT and high viral load, liver fibrosis assessment is needed if the patient is older (above 30 or 35 years old) or has family history of HCC. For truly immune-tolerant patients (with no significant fibrosis), the risk of disease progression is generally small. If NA treatment is started, complete viral suppression by NA may be difficult and off-treatment relapse is frequent. Evidence for long-term benefit of treatment is currently evolving. At this moment, regular monitoring is therefore recommended by all key international guidelines.

## Authorship Statement

The author was responsible for the interpretation of data, the drafting, and critical revision of the manuscript for important intellectual content.

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## Conflicts of Interest

Grace Wong has served as an advisory committee member for Gilead. She has also served as a speaker for Abbott, Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead, Janssen, and Roche.

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