COMMENTARY

Perspectives on Outcome Prediction in Patients With Chronic Hepatitis B Virus Infection

Introduction

Chronic hepatitis B virus (HBV) infection is a serious global health issue because of its potential adverse outcomes, including hepatic decompensation, liver cirrhosis, and/or hepatocellular carcinoma (HCC) development.[1] Since the advent of effective anti-HBV agents, selection of proper patients for long-term nucleos(t)ide analog (Nuc) therapy has become an important clinical issue. All updated HBV guidelines agree that patients with significant hepatitis activity, represented by serum alanine aminotransferase (ALT) elevation to >2 times the upper limit of normal (ULN) and/or significant hepatitis fibrosis, are candidates for antiviral therapy.[2–4] These include hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB), HBeAg-negative CHB, and HBV-LC (LC: liver cirrhosis). Given that Nuc once a day is convenient, highly effective in HBV suppression and virtually no immediate side effect, emerging calls for expanding indication to almost all patients with viremia have attracted increasing discussion. For this, there are more and more reports on remote long-term prediction of outcomes, mostly relying on characteristics of patients at baseline or certain single time points.[5] However, HBV is not directly cytotoxic and liver injuries are immune-mediated. Hence, chronic HBV infection is a dynamic process of interactions between HBV and host immune cells on hepatocytes so that liver injuries may come and go or may change from active to inactive phase, and vice versa.[1,6] Whether predictions based on changeable marker(s) at single time point are plausible and whether combination or trajectory prediction models are more appropriate need to be reviewed.

Natural Course and Outcomes of Chronic Hepatitis B Virus (HBV) Infection

Studies have shown that chronic HBV infection starts from an HBeAg-positive immune tolerant phase (IT) with high serum HBV DNA (7.5–8.5 $\log_{10}$ IU/mL) and hepatitis B surface antigen (HBsAg) levels (4.5–5.0 $\log_{10}$ IU/mL), normal ALT and no or minimal hepatitis activity. Then, usually after adolescence, hepatitis activity may develop and enter the immune clearance or immune active phase (IA). During the IA phase, episodic ALT elevations with hepatitis (HBeAg-positive CHB), even hepatitis flares (ALT>5× ULN), may occur with decreasing HBV DNA/HBeAg/HBsAg levels and finally undergo HBeAg seroclearance/seroconversion into HBeAg-negative inactive carrier phase (IC) with low HBV DNA (<2000 IU/mL) and HBsAg (<1000 IU/mL), normal ALT, and quiescent hepatitis activity. HBsAg loss/seroclearance, a hallmark of functional cure, may occur after a long inactive phase at 1%–2% per year. Conversely, HBV may reactivate (reactive phase) with intermittent/persistent hepatitis (HBeAg-negative CHB) or hepatitis flare. The frequency, the severity, the extent and the duration of liver injuries during IA or reactive phase are determinants for the long-term outcomes. The outcomes of each of these phases are summarized in Table 1.[1,6]

Prediction in HBeAg-Positive Patients With CHB

One of the characteristics of CHB is the occurrence of episodic hepatitis flare (ALT>5× ULN). The ascending ALT of hepatitis B flares is usually preceded by a parallel rise of quantitative HBsAg (qHBsAg) and HBV DNA levels.[7] A few (<5%) hepatitis flares may be very severe and deteriorate to hepatic decompensation which is a critical safety concern requiring immediate management because the risk of hepatic failure or even fatality. A study in non-cirrhotic patients showed that hepatitis flare with an HBV DNA level $>3 \times 10^8$ IU/mL may predict subsequent hepatic decompensation at a sensitivity of 86%, a specificity of 86%, and a negative predictive value (NPV) of 99% though a positive predictive value (PPV) of only 24%.[8] To ensure safety, immediate Nuc therapy is required for such flares.

Fortunately, most of the hepatitis flares may resolve spontaneously in association with HBV DNA/HBV antigens decline. As summarized in a review article,[7] studies have shown that hepatitis flare may be followed by HBeAg seroclearance within 1 year in >50% of the patients whereas the 1-year rate was only 5% in those with ALT <5× ULN ($P < .001$). In addition, patients with ALT >10× ULN showed significantly higher rates of HBeAg seroclearance within 3 and 6 months than those with ALT of 5–10× ULN (25 vs 5%, $P < .001$ and 34 vs 20%, $P = .03$, respectively) but no significant difference in 12 months rate (52 vs 45%, $P = .3$). Furthermore, the alpha-fetoprotein (AFP) level may increase to its peak mostly 1–2 weeks after the peak ALT during hepatitis flares. Flares with AFP>100 ng/mL are closely correlated with histologic findings of bridging hepatic necrosis (BHN) and may be followed by spontaneous HBeAg seroclearance within 3, 6, and 12 months in 31%, 45%, and 62%, all significantly higher than 4%, 6% and 15%, in hepatitis flares with AFP <100 ng/mL, respectively. Likewise, the rate of spontaneous HBeAg seroclearance/seroconversion within 12 months was significantly higher in hepatitis flares with BHN (67%) than 16% in those with lobular hepatitis but no BHN.[7]

Table 1. Long-Term Outcomes of Chronic HBV Infection

Phases	HBeAg	Hepatitis	Outcomes (% per year) LC	HCC	HBsAg loss
IT (PNALT)	+	No	0	0	0
↓					
IA	+	CHB	2–4	~0.8	0
↓					
IC (PNALT)	–	Quiescent	0.06	<0.1	1–2
↓					
Reactive	–	CHB	2–3	~0.4	0
LC	+ or –	Variable	NA	3–6	1.5

CHB, chronic hepatitis B; IA, immune active; IC, inactive carrier; IT, immune tolerance; HCC, hepatocellular carcinoma; LC, liver cirrhosis; NA, not applicable; PNALT, persistently normal alanine aminotransferase.

In brief summary, HBeAg-positive hepatitis flare with an HBV DNA level of 3×10^8 IU/mL may predict hepatic decompensation in days to weeks, whereas a flare with ALT >10× ULN or ALT>5× ULN plus a rising AFP >100 ng/mL and/or BHN may predict spontaneous HBeAg seroclearance in months (Table 2). These short-term predictors are useful and applicable in daily clinical decisions. For example, it has been recommended to monitor HBeAg-positive CHB with hepatitis flare up to 3 months for possible spontaneous HBeAg seroclearance or the need for antiviral therapy.[1,7]

Prediction in HBeAg-Negative Patients

Quantitative HBsAg (qHBsAg) has been considered as a surrogate marker of hepatocytes containing covalently closed circular DNA (cccDNA) and/or integrated DNA (iDNA). It has been widely used in patients with chronic HBV infection since the early 2010s. Since ~90% of qHBsAg in HBeAg-negative patients are transcribed from iDNA,[19] qHBsAg assay is particularly important and useful for patients in HBeAg-negative phases.[6]

Table 2. Plausible Outcome Prediction in Chronic HBV Infection

I HBeAg-positive hepatitis B flare
- 1 Hepatic decompensation (in days–weeks)
  - a HBV DNA of 3×10^8 IU/mL: NPV: 99% PPV: 24%[8]
- 2 HBeAg seroclearance (in 3 mo) [summarized in ref[7]]
  - a ALT>10 ULN vs 5–10×: 25% vs 5%; b. flare with AFP >100 vs <100 ng/mL: 31% vs 4%
- 3 HBeAg seroclearance (in 12 mo) [summarized in ref[7]]
  - a Flare with AFP >100 vs <100 ng/mL: 62 vs 15%; with BHN: Yes vs No: 67 vs 16%

II HBeAg-negative IC/GZ
- 1 Differentiation of hepatitis B flares in days–weeks: combined qHBsAg/ALT kinetics[9]
- 2 Transition to HBeAg-negative IA (based on follow-up data), summarized in [ref[10]]
  - a 5 y: IC[a]: 0, GZ: 2.2%; 5–8 y: IC[a]: 0, GZ: 12%
  - b Normal ALT + qHBsAg>1000 IU/mL + HBV DNA>200 IU/mL: NPV: 96%[11]
- 3 HBsAg loss in 5–10 y
  - a IC[a]: 20%; GZ: 12% (based on follow-up data), summarized in [ref[10]]
  - b qHBsAg <100 IU/mL in ICs[12,13]
- 4 HBsAg loss in 1–3 y; qHBsAg <200 IU/mL + 1-y decline >0.5 log IU/mL[14–16]

III Long-term predictions for LC and/or HCC (based on >10-y follow-up data)
- 1 HBV DNA declined to <2000 IU/mL: lowest risk (Hazard ratio 1 vs 3.12–16.78)[17]
- 2 PNALT: lowest risk for HCC vs ALT>2× ULN: ~20×[18]

AFP, alphafetoprotein; ALT, alanine aminotransferase; BHN, bridging hepatic necrosis; GZ, gray zone; IA, immune active phase; IC, inactive carrier phase; NPV, negative predictive value; PNALT, persistently normal ALT; PPV, positive predictive value; ULN, upper limit of normal.
[a]IC, defined by 3-combined criteria (ALT < ULN + HBsAg <1000 IU/mL + HBV DNA <2000 IU/mL); [ ]: reference.

Inactive HBsAg Carriers

A study in genotype D HBV-infected patients showed that qHBsAg <1000 IU/mL combined with HBV DNA <2000 IU/mL and normal ALT at a single time point had an NPV of 97% and a PPV of 88% to identify ICs.[20] A long-term follow-up study in genotype B and C HBV-infected subjects have also shown that these 3 combined criteria are adequate in predicting future IC with a sensitivity of 71% and a specificity of 85%.[12] Conversely, in patients with normal ALT, combined qHBsAg >1000 IU/mL and HBV DNA >200 IU/mL may predict subsequent HBV reactivation at an NPV of 96%.[11]

In ICs, it was further shown that a single time point qHBsAg <100 IU/mL could predict HBsAg loss in 5–10 years,[12,13] and hepatitis B core-related antigen (HBcrAg) <10,000 U/mL in patients with HBsAg >1000 IU/mL may predict HBsAg loss in 10–14 years.[13] Instead of such remote long-term prediction, qHBsAg <200 IU/mL in HBeAg-negative patients with persistently normal ALT was found to be an optimal threshold level toward HBsAg loss in 1 and 3 years with an NPV of 100% and 92% and an PPV of 35% and 49%, respectively. Notably, these PPVs may increase to 97% and 100%, respectively, if the patient had a precipitous HBsAg decline >1 $\log_{10}$ IU/mL (>90%) decline in the preceding 2 years or >0.5 $\log_{10}$ IU/mL (>70%) decline in 1 year.[14] Such prediction is also applicable for off-therapy HBsAg loss.[15] Another study also showed a qHBsAg <200 IU/mL plus a decline >0.5 $\log_{10}$ IU/mL (>70%) in the following 1 year predicted HBsAg loss in 3 years with a sensitivity of 74.1% and a specificity of 89.4%.[16] Conceivably, 1–3 year prediction of HBsAg loss is much more

practical than >5–10 years remote long-term prediction in forecasting prognosis.

HBeAg-Negative Patients With CHB

Similar to HBeAg-positive CHB, HBeAg-negative CHB is also characterized by episodic ALT elevation and hepatitis flares as result of immune-mediated hepatocytolysis.[7] Given that ~90% of serum HBsAg are transcribed from iDNA and Nuc therapy can interrupt new iDNA but not decrease existing iDNA,[19] it was postulated that qHBsAg started to decline from the level at the preceding days to weeks might represent decreasing level of covalently closed circular DNA and/or iDNA, possibly due to the death of infected hepatocyte and dilution by regeneration of uninfected hepatocyte as well as the effect of noncytolytic viral clearance by cytokines. Flares with such dynamic qHBsAg changes may lead to spontaneous resolution with a certain degree of HBV clearance within a few weeks ~ months. Hepatitis flares with such "good" and "beneficial" results reflect the dominance of the effective host immune response over HBV, hence was called "host-dominating flares".[9] In contrast, qHBsAg increases further or remains high along with the ascending ALT to its peak might represent increasing iDNA due to high viremia and hepatitis activity induced frequent double-stranded DNA break-point.[19] Flares with such qHBsAg changes would lead to persistent/intermittent hepatitis or even worse outcomes in weeks to months. Hepatitis flares with such "bad" or "detrimental" results may reflect the dominance of HBV over the ineffective host immune response, hence was called "virus-dominating flares".[9] Such combined HBsAg/ALT kinetics can differentiate these 2 types of hepatitis flare and predict who requires anti-HBV therapy. A retrospective appraisal has confirmed the predictions that patients with a "bad" virus-dominating flare have a "good" response to Nuc therapy with HBsAg decline >1 $\log_{10}$ IU/mL (>90%) in 12 months whereas the patients with "good" host-dominating flare have a "bad" response to Nuc therapy with only −0.01 $\log_{10}$ HBsAg decline in 1 year or even HBsAg rebound >2-fold and no HBsAg loss, in contrast to 21% 3-year HBsAg loss in those remained untreated.[21] Conceivably, such short-term (days to 3 months) prediction by dynamic changes of qHBsAg/ALT is useful and beneficial in clinical practice.

Remote Prediction for Long-Term Adverse Outcome: Static vs Dynamic Factor(s)

It has long been documented that age, male, HBV genotype/mutation, age at HBeAg seroconversion, hepatitis C and/or hepatitis D superinfection, and advanced fibrosis are factors for the development of adverse outcomes.[1] Remote long-term prediction using one or more of these "static" factors at a single time point is plausible. However, the clinical phases, serum levels of ALT, HBV DNA, HBeAg, and qHBsAg may change over time. Remote long-term predictions using these changeable factor(s) at a single time point could be wrong and not valid or misleading because immune-mediated changes may occur during the intervals between follow-up visits and the long duration from starting point to the endpoint of the study. The famous REVEAL HBV study (the Risk Evaluation of Viral Load Elevation and Association Liver Disease/Carrier Hepatitis B Virus) is the best example of this kind of remote prediction. The study concluded that the cirrhosis and/or HCC risks start to increase at a baseline serum HBV DNA level of 10^4 copies/mL in a dose-dependent manner, independent of other baseline factors.[22] Thereafter, HBV DNA of 10^4 copies/mL (approximately 2000 IU/mL) has been widely adopted as a threshold for anti-HBV therapy.[2–4] However, the REVEAL study group later demonstrated that subjects with spontaneous HBV DNA reduction from higher levels to <10^4 copies/mL had a similar risk of HCC to those with a baseline HBV DNA <10^4 copies/mL.[17] These findings indicate that a changeable factor at a single time point is not plausible for remote long-term prediction. Likewise, baseline HBcrAg of 10,000 U/mL reported as remote predictors for HCC development over 10 years[23] is not plausible without including data changes overtime. A single time point serum ALT level is also not appropriate to define the IT or IC phase and for remote long-term risk prediction of hepatic decompensation, cirrhosis, HCC, and mortality. In contrast, long-term studies with multiple ALT measurement have shown that elevation of serum ALT to >2× ULN during the course of an IC significantly increase the risk of adverse outcomes.[18] Clearly, remote long-term prediction by these changeable "predictors" at a single time-point is not reliable.

Follow-up studies have shown little fibrosis/disease progression in HBeAg-positive IT and HBeAg-negative ICs with persistently normal ALT. HBsAg carriers with ALT of 1-2× ULN and/or HBV DNA (Gary-zone) have similar excellent long-term (5–9 years) prognosis to ICs with a high rate of HBsAg loss and low rate of developing HBeAg-negative CHB, as reviewed elsewhere[10] and shown in Table 2. Several more recent studies provided data to support expanding the indication of therapy to include IT phase patients and those at the indeterminate phase or Gray zone. Unfortunately, these recent studies either relied on a single time-point factor or a phase and neglected that clinical phases may change over time and that events during IA or reactive phase are the real determinants for disease progression.[5,10] For example, a study involving 413 patients showed that IT patients had a 2-fold higher risk (10-year: 12.7 vs 6.1%) of HCC than IA patients on long-term antiviral therapy and thus proposed to start anti-HBV therapy early for IT patients.[24] However, the study showed extensive overlapping of the baseline features between their IT and IA patients that might have misclassified their IT patients and have

neglected the fact that the patients in the IT phase must have transitioned to the IA phase and would then be treated to prevent/reduce disease progression including HCC.[10] Similarly, a recent study involving 855 untreated patients of the indeterminate phase showed only 2% transitioned to IA phase in 10 years but 14.7% developed HCC in this period, hence proposed expansion of treatment indication to patients in the indeterminate phase.[25] However, compared with those of the earlier long-term follow-up studies including their own, the study had problems leading to a transition rate too low and an HCC rate too high to be acceptable/reliable.

Summary and Conclusion

In conclusion, combined criteria at a single time point, namely HBeAg-positive hepatitis flare with AFP and/or BHN, qHBsAg + HBV DNA + ALT in HBeAg-negative ICs and dynamic qHBsAg changes in HBeAg-negative hepatitis flares are plausible for prediction within 12 months. Baseline static factors, such as sex and HBV genotypes, may be used for remote long-term prediction. However, single time-point changeable biomarkers, such as HBV DNA, qHBsAg, and HBcrAg, are not appropriate for remote outcome prediction in chronic HBV infection. Therefore, instead of expansion of treatment indication to include patients in IT, indeterminate phase or gray zone, proper monitoring of such patients, namely 3-monthly for HBeAg-positive/6-monthly for HBeAg-negative patients with normal ALT and more frequently upon ALT elevation plus HCC surveillance using AFP and ultrasongraphy/3–6 months, is the key to detect phase change, hepatitis activity or HCC timely and start relevant therapy where appropriate.

Further studies on the prediction of a dynamic disease entity need to take into account such pitfalls. On the other hand, it is advisable to be more critical/skeptical, especially on the methodology and biological plausibility, when running into controversial finding(s).

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