Review Article

Current perspectives into the evaluation and management of hepatitis B: a review

Vignan Manne, Eric Gochanour, Kris V. Kowdley

Liver Care Network, Swedish Medical Center, Seattle, WA, USA

Correspondence to: Kris V. Kowdley. Liver Care Network, Swedish Medical Center, Seattle, WA, USA. Email: kris.kowdley@swedish.org.

Abstract: Hepatitis B is a widespread disease which affects millions of people worldwide. Chronic hepatitis B (CHB) can lead to significant morbidity and mortality due to complications such as cirrhosis and hepatocellular carcinoma. The pathophysiology of hepatitis is critical to diagnosing CHB. Deciding which patients with CHB should be treated is an important decision as treatment can often lead to better outcomes in the appropriate patient population. The nucleos(t)ide analog inhibitors entecavir and tenofovir are currently the mainstay of treatment as they are able to successfully suppress the virus and lead to fewer complications. Novel therapies are currently being developed which may offer a potential cure for this disease in the future.

Keywords: Chronic hepatitis B (CHB); hepatocellular carcinoma (HCC); tenofovir; entecavir

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Introduction

Hepatitis B infection is a common cause of chronic liver disease. The World Health Organization (WHO) estimates that 257 million people are living with hepatitis B (1). In 2015, over 800,000 deaths worldwide were attributed to complications of hepatitis B infection; the majority of which were related to complications of chronic infection such as the development of cirrhosis and hepatocellular carcinoma (HCC) (1). The significant morbidity and mortality associated with chronic hepatitis B (CHB) has led to a flurry of research and advances in understanding the pathophysiology and natural history of the infection. This knowledge has led to development of novel therapies for treatment. This article is aimed at reviewing characteristics of HBV, its impact on development of HCC, the criteria for treatment of CHB, and current first-line and future therapies.

HBV characteristics

The hepatitis B virus (HBV) is composed of a partially double-stranded DNA genome packaged with an HBV polymerase (2). The genome is covered by a protein capsid, the so-called hepatitis B core antigen (HBcAg), which is then enclosed in a lipid bilayer that contains surface proteins, the hepatitis B surface antigen (HBsAg) (2). The HBsAg assists the virus particle in gaining entry into hepatocytes (2). Once the virus infects a hepatocyte, the partially double-stranded DNA is transformed into a stable circular form called covalently closed circular DNA (cccDNA) (3). The cccDNA is very stable and a difficult to eradicate form of the HBV genome that resides in the hepatocyte for the life of the cell (3). Replication of the virus consists of transcription of the cccDNA into pre-genomic RNA that is reverse transcribed to HBV DNA before being packaged into another viral particle (4).

Several key areas of the HBV genome with clinical relevance beyond viral assembly are the core and precore regions. These regions are involved in assembly of the HBcAg and the Hepatitis B e-antigen (HBeAg) (3). The precore region is transcribed into precore mRNA that is translated into a single peptide, which is than cleaved to form HBeAg (2). The function of HBeAg is still not well defined but mutations involving the precore region are associated with the development of HBeAg-negative chronic

Table 1 CHB serologic interpretation

Variables	HBsAg	HBeAg	HBV DNA	Anti-HBe
Inactive CHB**	+	–	–	+
HBeAg-positive CHB*	+	+	+/++	–
HBeAg-negative CHB*	+	–	+/++	+
Immune-tolerant CHB**	+	+	+++	–
Immune-active CHB***	+	+/–	++/+++	+/–

*, serum ALT levels can fluctuate from normal to abnormal; **, serum ALT levels are normal in these cases; ***, serum ALT levels are elevated.

hepatitis B (5,6). There is also an increased likelihood of seroconversion of HBeAg or going from HBeAg positive to HBeAg negative with anti-HBe (5,6). Despite increased rates of seroconversion and lower levels of viremia, HBeAg-negative hepatitis B with precore mutations is associated with older individuals and more advanced liver disease (7). The core region is also associated with advanced liver disease, as well as an increased risk of HCC, but mutations in the core region are not as firmly correlated with HBeAg-negative HBV as precore mutations (8,9). Identifying variants of the core and precore regions is not standard practice when evaluating which patients require treatment; however, it can be useful in stratifying patients who are at highest risk of progression of CHB to cirrhosis (10).

In addition to the mutations in the core/precore regions of the HBV genome, there are many different genotypes of HBV, and several subtypes within each genotype (11). These genotypes are lettered from A to J and generally have a unique geographical distribution (11). Similar to the precore/core mutations, the clinical utility of identifying the HBV genotype can provide further information on the risk of disease progression and development of HCC (10,11). For example, genotype B has been associated with a milder form of chronic hepatitis B with slower progression of disease and a higher likelihood of HBeAg seroconversion when compared with genotype C (12). Genotype testing is not yet standard of care but can help guide treatment considerations and monitoring for CHB.

Diagnosis of HBV infection

Serological markers are the primary method by which infection with HBV is diagnosed. The presence of HBsAg is diagnostic of infection and if present for more than 6 months is indicative of chronic infection. Multiple phases of CHB have been identified, each with its own treatment implications (10,13,14). These are listed in *Table 1*.

Screening for HBV is recommended in areas where prevalence is considered high (>2% prevalence) (4). The risk of developing CHB varies by age with infants less than 1 year of age having a >80% chance of developing CHB whereas toddlers between 1 and 6 years have between a 30–50% risk (1). Less than 5% of adults with an acute infection will develop CHB but close to a third of these patients who acquire CHB will develop advanced liver disease and/or HCC (1).

Risk factors for progression of HBV chronic liver disease

Several risk factors for progression of CHB to cirrhosis have been identified. HBV DNA level in blood, specifically a level $>10^4$ copies/mL, was one of the strongest predictors of progression to cirrhosis (15). This was independent of ALT, HBeAg status, age, and other factors (15). Older age is also a strong predictor of progression, but this is more likely due longer duration of disease rather than an independent risk factor (16). Another commonly associated risk factor is male sex although the exact mechanism is not well understood (16).

The overall incidence of cirrhosis in patients with HBeAg-positive hepatitis B was 1.6 and 3.8 per 100 person-years in East Asian and European countries, respectively (16). In patients with HBeAg-negative chronic hepatitis B the incidence was 2.8 and 9.7 for the same East Asian and European countries, respectively (16). The incidence in per 100 person-years roughly corresponds to a 5-year cumulative incidence of 8% and 17% in the HBeAg-positive CHB compared to a 5-year incidence of 13% and 38% in HBeAg-negative CHB in East Asian and European countries, respectively (16). While this seems to indicate that HBeAg-negative CHB is a risk factor for progression to

cirrhosis, this is also likely related to duration of disease (16). Other risk factors associated with increased progression to cirrhosis include HBV genotype, presence of co-infections of hepatitis C or hepatitis D, and presence of other chronic liver diseases such as non-alcohol steatohepatitis (NASH) (16).

Liver cancer and HBV

HBV is the most common cause of HCC, being responsible for >50% of cases worldwide (17). The relative risk of developing HCC increases by 15–20-fold in patients with HBV compared to uninfected patients (18) with an annual incidence of HCC in hepatitis B carriers of 0.5% (19,20). It is thought that 10–16% of patients with HCC in the US are infected with HBV (21).

HBV is unique in that patients with the disease are at increased risk of developing HCC, even in the absence of cirrhosis. This is in contrast to chronic hepatitis C and other causes of liver disease where cirrhosis is a prerequisite to the development of HCC. The pathogenesis of HBV is distinctive because HBV initiates hepatic carcinogenesis by gaining entry into hepatocytes leading to integration into the host genome with subsequent alteration of the host DNA/RNA (22). This can cause structural alterations, sequence variations, deletions and inhibition of tumor suppressor genes leading to the development of cancer (23-26). Of note, Liu *et al.* showed risk factors for development of HCC in the setting of HBV in the absence of cirrhosis was associated with male gender and higher viral loads (27). HBV genotype also appears to play a role as studies have shown that genotype C and F CHB patients are more likely to develop HCC when compared to other genotypes (28,29). In addition, the basal core promoter T1762/A1764 mutation has been directly linked to the development of HCC (27).

Due to this increased risk of developing HCC, certain patient populations infected with HBV should undergo surveillance for HCC. Screening options include regular blood work including liver function tests, alpha-fetoprotein (AFP) and abdominal ultrasound every 6 months. Patients at increased risk include Asian men >40, Asian women >50 and all patients with cirrhosis regardless of age (30). In addition, patients should receive extra consideration for screening if they meet any of the following criteria: patients with a first degree relative with HCC, African patients, patients co-infected with HIV or HCV and patients with evidence of active disease (30). Stratifying those patients with CHB at highest risk for HCC is still unclear and has led to multiple scoring models designed to assess this risk. These include the individual prediction model (IPM), CU-HCC score, GAG-HCC score, NGM1-HCC, NGM2-HCC, REACH-B score and the PAGE-B score (31). While the initial models were not fully validated, more recently developed models have shown more promise and multiple have now been validated and are currently in use (31).

The CAMD scoring system was created by Hsu *et al.* to assess the risk of development of HCC in patients with HBV undergoing treatment with antiviral therapy (32). This score was created using a Taiwanese cohort and validated by a Hong Kong cohort, the scoring system uses readily available information (cirrhosis, age, male sex and presence of type 2 diabetes mellitus) to stratify patients into low, intermediate and high-risk groups (32). Based on the results of this study, the authors concluded that the low and high-risk groups had distinctly different risks of developing HCC (32). The risk of HCC was so small in the low-risk group, annual incidence of 0.3%, that the need to adhere to current screening guidelines was questioned but no formal recommendations were made (32).

The risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B) score is another validated scoring system used to predict risk of HCC in patients with CHB without cirrhosis (33,34) Developed using a Chinese cohort and validated in separate cohorts from Hong Kong and South Korea, this score used age, sex, HBeAg status, HBV DNA and alanine aminotransferase levels in patients without cirrhosis to assess the risk of developing HCC (33,34). Ultimately, the 17-point risk score was able to reliably predict the likelihood of developing HCC at 3, 5 and 10 years (33,34). A revised version of REACH-B, which incorporated HBsAg levels, has also been developed to provide further clarification of high-risk groups (35).

While previous scoring systems focused mainly on Asian population, the PAGE-B score was developed in attempt to risk-stratify Caucasian patients with CHB being treated with antiviral therapy (36). This scoring system incorporates only three factors (age, gender and platelets) and was developed using a derivation and validation group in patients taking modern antiviral therapies (entecavir and tenofovir) (36). A modified PAGE-B score has subsequently been created to identify CHB at risk of developing HCC in Asian populations (37). Overall, being able to predict which patients with CHB are most likely to develop HCC allows providers to focus surveillance on the groups at highest risk.

Although treating CHB does not completely eliminate the risk of getting HCC, it does significantly lower the

chance of developing it. A study published by Nguyen et al found that treatment with tenofovir in patients with CHB, with or without cirrhosis, decreased the risk of developing HCC from 20.13% for the untreated group compared to 4.69% in the treated group over an 8-year period (38).

There are multiple treatment options for patients with HBV who do develop HCC. These include ablation (radiofrequency ablation or the injection of ethanol), embolization (chemoembolization vs radioembolization), radiation, resection and liver transplantation (30,39). It has recently been demonstrated that patients treated for HBV prior to partial liver resection have better outcomes including lower incidence of microvascular invasion and reduced risk of early cancer recurrence (40). Immunotherapy and chemotherapy are the last line of treatment as palliative measures for metastatic disease (30). The specific type of treatment will depend on the size of the tumor, whether there are one or multiple tumors, local experience with the different modalities and the presence/absence of widespread disease.

Criteria for treatment

Patients with CHB have higher rates of many liver-related complications including cirrhosis and HCC. Due to the stability of cccDNA, the eradication and cure of hepatitis B is extremely difficult. This difficulty has led to a paradigm shift in chronic hepatitis B treatment, from the goal of eliminating the virus to suppressing viral replication. When considering viral suppression, not all patient populations have a shown long-term benefit, such as decreased liver-related complications of CHB (10). Because of this careful selection when considering treatment is important (10). Thus, the decision to treat patients with CHB is critical as treatment will ultimately lead to significant improvement of health outcomes in those populations who meet criteria.

The three main criteria used to determine if a patient should be treated for CHB are serum HBV DNA levels, serum ALT levels and the severity of liver disease (10,12,13). Other factors that should be considered are age, overall health status, family history of HCC or cirrhosis and extrahepatic manifestations of disease (10,12,13).

Currently, differentiating between immune-active and immune-tolerant states of chronic hepatitis B has important treatment implications, though this may change in the future (*Table 1*) (10). Immune-active CHB is defined as ALT levels ≥2 the upper limit of normal (ULN), defined as >35 U/L for men and >25 U/L for women, or significant histological evidence of disease plus elevated HBV DNA (above 2,000 IU/mL for HBeAg negative or above 20,000 IU/mL for HBeAG positive patients) (10). It is worth noting that the indication for treatment is mostly independent of HBeAg status (10,12,13).

Antiviral therapy is currently recommended for immune-active CHB to reduce the risk of liver related complications of the disease (10). Additionally, all patients with decompensated or compensated cirrhosis who are HBsAg-positive should be treated regardless of HBV DNA level, ALT level or HBeAG status (10). In contrast, treatment is not recommended for patients with immune-tolerant CHB as the risk of developing complications is thought to be much lower in this population (10).

Other patients with CHB to consider treating include HBsAg-positive pregnant women but only if the HBV-DNA level is >200,000 IU/mL (10). Treatment is recommended to decrease the risk of perinatal transmission, especially because the risk of CHB is very high for infants despite vaccination and hepatitis B immunoglobulin (HBIG) (10). Patients with chronic HBV who plan to start immunosuppression therapy for any reason should also be treated to prevent a reactivation flare.

Prior studies have shown that patients with CHB who have significantly elevated HBV DNA (>20,000 IU/mL) are at increased risk for developing HCC and cirrhosis regardless of ALT levels (15,41). Despite this, current guidelines do not recommend treatment of immune-tolerant patients with high HBV DNA levels (10,13). A new study by Kim *et al.* demonstrated that this population may actually benefit from receiving early treatment (42). In this study, the authors found that immune-tolerant patients who were not treated for CHB had a higher risk for HCC, death and need for liver transplant compared to patients with immune-active disease treated with antiviral therapy (42). Moreover, in patients with mildly active disease (ALT levels 1–2× the ULN), the risk of HCC, death and need for liver transplant were increased even further (42). Based on these results, the authors surmised that many occurrences of HCC, transplantation and death could be avoided by treatment of CHB during the immune-tolerant phase (42). While current guidelines continue have not yet changed based on this data, with more research on the topic the guidelines may change in the future.

Adherence to treatment is as important as careful selection of patients who meet criteria for treatment. A recent 10-year longitudinal observational study by Shin et al demonstrated this by showing that patients who were non-

adherent to treatment had an increased risk of complications from cirrhosis, HCC, and mortality when compared with patients with adherence rates of 90% or higher (43). Specifically, patients with adherence rates <90% had a 2.9 times higher rate of both cirrhotic complications and HCC (43). These patients also had a significant increase in liver-related (14.3-fold) and all-cause mortality (5-fold) (43). Not surprisingly, patients with good adherence rate also had a higher rate of virologic response, maintained virologic response and had lower rates of virologic breakthrough (43).

Of note, patients who receive long-term treatment for CHB have similar overall and liver-related survival rates to those in the general population (except those with HCC) over an 8-year follow up period (44). Patients who received treatment also had improvement in histological findings of fibrosis and reversal of early liver decompensation (36). These findings again support the need for treating patients with CHB.

Despite the mounting evidence of improved outcomes of patients with CHB who receive treatment, global treatment rates remain low (45). In 2016, only one in six patients diagnosed with HBV worldwide received treatment (45). This is somewhat surprising given the international market price of the two most common HBV medications (tenofovir and entecavir) has decreased significantly in recent years (45). For example, the price of generic tenofovir declined 85% from 2004 to 2016 (45).

Overall, treatment of patients with CHB is critical to help control this disease. Knowing who to treat is a vital aspect. Also, those who are treated should be monitored closely for adherence. These habits will lead to better outcomes and longer lives for patients living with this disease.

Treatment options

The treatment for CHB has evolved dramatically over the last 3 decades. The first known therapy for CHB was interferon-α (IFN-α) that was introduced in the early 1990s (46). Interestingly, it is the only known medication that can actively degrade cccDNA but the response rates to treatment are low with less than 10% ever testing negative for HBsAg and less than 50% demonstrating viral suppression (10). Furthermore, the severity of adverse side effects associated with IFN precluded the use of this therapy for all populations (47). The paradigm shifts away from complete elimination of the virus to suppression led to the introduction of nucleos(t)ide analog inhibitors (NAIs).

The introduction of Lamivudine (LAM) in 1998 presented an oral regimen that was highly effective at suppressing viral load, which subsequently decreased liver-related morbidity and mortality (48). Unfortunately, data indicated that HBV would quickly develop resistance to LAM after as little as 1 year of therapy (49). Indeed, in a 5-year study, the incidence of LAM resistance increased from 23% at 1 year to 65% in 5 years (49). Moreover, longer duration of therapy led to increased risk of resistance development (49). Following the addition of LAM, several other therapies have been developed but the current first-line medications have largely supplanted all other available treatment options (10,13). This is primarily due to the high genetic barrier for resistance development in HBV (48).

There are 3 current first-line treatment options: entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF). Since eradication of HBV is not universally feasible with current therapies, other endpoints are used to monitor efficacy of treatment for CHB. These markers include normalization of serum ALT, HBeAg seroconversion, and HBV DNA suppression (10).

Entecavir (ETV)

Entecavir is a guanosine analog that leads to chain termination when incorporated into HBV DNA during replication (48). The effectiveness of ETV has been demonstrated in both HBeAg-positive and negative patients and has proven to have sustained long-term benefits in liver-related morbidity and mortality outcomes (50-52). The side effect profile of ETV is mostly benign with the most concerning side effect being the development of renal disease (53). While ETV does not appear to cause renal failure, it may lower the GFR and dose adjustment is required depending on degree of renal disease (53). Development of resistance to ETV has been documented and the risk of HBV resistance to ETV therapy was noted to be 1.2% after 5 years of therapy (54). This has led to the phrase 'high-genetic barrier of resistance' when describing ETV, as well as TAF/TDF. However, in patients who are LAM-experienced the risk of HBV resistance was noted to be 51% after 5 years as ETV is a pyrimidine analog similar to LAM (54). Therefore, in LAM-inexperienced patients, ETV can be considered first-line therapy in patients (10).

Tenofovir (TAF/TDF)

Tenofovir is an adenosine analog that, like ETV, leads to chain termination during HBV replication (48). Tenofovir disoproxil fumarate (TDF) was the first tenofovir formulation available and was FDA-approved for use on the basis of its efficacy when compared to a previously used agent named adefovir (55-57). The effectiveness of TDF is comparable to ETV, which is why either is acceptable as first-line therapy for CHB (10). Unlike ETV, there are no documented cases of resistance to TDF therapy (58). The side effect profile for TDF is also relatively benign except a small portion of patients who have developed drug-related decreased bone density as well as renal toxicity (55,59). Dosage adjustment is required in the setting of renal disease (55,56). The increased risk of osteopenia and renal toxicity led to the development of tenofovir alafenamide (TAF), which is noted to have the same efficacy of TDF but has a somewhat better safety profile (60).

Future therapies

Although current therapies for CHB are effective in suppressing the virus and causing normalization of ALT, there is currently no cure for HBV. Additionally, all first-line therapies require indefinite or prolonged treatment. Several novel therapies are under development that explore a variety of different treatment targets.

HBV entry inhibitors

One potential target currently being studied is inhibiting the entry of HBV particles into the hepatocyte. The viral particle does this through binding of specific proteins with the hepatocyte to gain entry (61,62). A compound has been developed, myrcludex B, that may inhibit viral entry by blocking the hepatocyte proteins required for HBV binding (63). A phase 1b/2a study was conducted in 24 patients co-infected with HBV and hepatitis D virus (HDV) which randomized patients to have either Myrcludex B, pegylated interferon α (PEG-IFN), or both and found that the use of myrcludex B with PEG-IFN was effective for viral suppression after 24 weeks (64). While these results are promising, the concern is that the drug acts on a bile acid transporter and may affect the non-infectious related function of the transport (64,65). In addition, this drug may require PEG-IFN to be effective however new compounds are being developed that may circumvent this issue (64,65).

Nucleocapsid assembly inhibition

The replication of HBV DNA occurs in nucleocapsids that are assembled prior to replication (66). Therefore, if the assembly of the nucelocapsid can be disrupted, the replication of viral DNA can be stopped (66). To that end, several compounds have been developed which are in preclinical or clinical development that act by either forming empty nucleocapsids which lack HBV DNA or non-capsid polymers (66). Using cellular models, these compounds have shown promising results in terms of antiviral activity (67,68).

DNA editing technologies

The advent of DNA-editing technology has funneled interest into development of a treatment that can specifically inactivate, or even eradicate, cccDNA from hepatocytes without damaging the hepatocyte chromosomes (66). The use of clustered, regularly interspaced short palindromic repeats (CRISPR)/CAS9 can edit the HBV cccDNA in a Hepatitis B-infected cell line (69,70). The specifics on how this can be translated into infected patients, as an efficient delivery system to infected hepatocytes, has not yet been developed and is still under investigation (66).

Conclusions

Treating CHB has become the next frontier in the treatment of viral hepatitis after the highly effective antiviral cure for hepatitis C has become readily available. CHB afflicts millions worldwide and understanding the pathophysiology and natural history of the disease has important screening and treatment implications for the disease. Current therapies are effective in suppressing the viral replication and improving liver-related outcomes but no virological cure has yet become available. New and exciting research in the field holds promise in preventing viral replications and hopefully can lead to a cure for this disease.

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None.

Footnote

Conflicts of Interest: KV Kowdley: Advisory Board: Gilead, Mavupharma; Consultant: Gilead; Speaker Bureau: Gilead.

V Manne and E Gochanour have no conflicts of interest to declare.

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