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Treatment of Chronic Hepatitis B: An Update and Prospect for Cure

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Abstract

Since the discovery of the hepatitis B virus (HBV) by Blumberg et al., nearly half a century ago, the subsequent development of a vaccine, understanding of the pathogenesis, and the advent of antiviral drugs, the prevalence of chronic hepatitis B has decreased from approximately 5% to 3.61% of the worldwide population. Despite this improvement, approximately 248 million individuals are still infected with the virus. Effective treatment of chronic hepatitis B is extremely important as a positive correlation has been observed between baseline viral load and the risk for the development of hepatocellular carcinoma (HCC). While there have been significant advancements in the management of hepatitis B virus with available nucleos(t)ide analogues, there remains much work to be done to prevent HCC. The molecular mechanism and the subsequent carcinogenesis and progression of chronic HBV carriers to HCC remain in large part poorly understood. While current treatment with nucleos(t)ide analogues has succeeded in maintaining undetectable viral levels in patients with chronic hepatitis B, eradication of the virus has not been possible, and there remains the risk of development of HCC. Therefore, more effective treatment regimens aiming for HBV cure are urgently needed. With multiple new therapies in the pipeline, the future of treating hepatitis B is an exciting and developing one, and hopefully, it will soon become a disease of the past.

Keywords: hepatitis B, hepatocellular carcinoma, anti-HBV drugs, nucleos(t)ide analogues, HBV cure, HBV therapy

1. Introduction

In the past 50 years, since the discovery of the hepatitis B virus [1], the development of a vaccine, understanding of the pathogenesis, and the advent of antiviral drugs, the prevalence of chronic hepatitis B has decreased from approximately 5% to 3.61% of the worldwide
population [2]. Nevertheless, hepatitis B remains a common and frequently encountered condition, affecting approximately 248 million individuals in the world.

The vast majority of individuals with chronic hepatitis B are located in Africa and Eastern Asia. In the United States, over 2 million Americans are afflicted and the majority (1.5 million) are immigrants from foreign countries [3, 4]. Effective treatment of chronic hepatitis B remains of extremely high importance, as patients who have been found to have higher baseline viral loads have been shown to have increased rates of hepatocellular carcinoma (HCC) [5]. As the treatment landscape of hepatitis B has shifted from earlier regimens of interferon and lamivudine to newer agents, namely tenofovir and entecavir, there remains much work to be done to reduce viral loads in patients and prevent long-term sequelae of cirrhosis and HCC. This chapter will discuss the natural history and potential carcinogenesis of hepatitis B virus, and will discuss current and possible future treatments, and the hope for an eventual cure.

2. Natural history of hepatitis B virus

In contrast to many known pathogens, hepatitis B virus (HBV) is not directly cytopathic to hepatocytes. Although not completely understood, the injury to the liver cells is in part through a host immune mechanism. Replicating HBV in hepatocytes produces HBsAg particles and virions which are taken up by the antigen presenting cells. The viral proteins are degraded to peptides, which are presented on the cell surface bound to MHC class I or II molecules. MHC class I molecules are recognized by CD8 T cells and MHC II by CD4 T cells. Virus-specific CD8+ cytotoxic T cells, with help from CD4+ T cells, recognize viral antigens presented on MHC class I chains on infected hepatocytes. This recognition reaction can lead to either direct lysis of the infected hepatocyte or the release of interferon-γ and TNF-α, which can down-regulate viral replication in surrounding hepatocytes without direct cell killing [6].

In order to further discuss advancements in the understanding and treatment of HBV, it is important first to review the natural history of the disease. The cycle of chronic HBV infection primarily consists of five phases as shown in Figure 1 [7, 8].

In the initial infection phase, or so-called immune tolerant phase, patients have very minimal inflammation. The hallmark of this phase is that these patients are found to be positive for HBeAg with high viral loads, typically >20,000 IU/mL (>10⁵ copies/mL) [9]. Conversely, they have normal aminotransferase (ALT) levels, and near-normal liver parenchyma on biopsy [10]. This “immune tolerant” phase is relatively short when HBV is acquired in adulthood, but can be sustained for much longer periods of time with infections acquired at birth or in early childhood [11, 12]. The risk of progressing to the chronic carrier state is significantly higher in infections acquired at a younger age, including up to a 90% risk when infected perinatally, as compared to a less than 1% risk of progression when acquired as an adult [13, 14].
Following the “immune tolerant” phase, patients progress into the “immune clearance” phase, which again consists of high viral loads and a persistently positive HBeAg. However, at this point patients begin experiencing increased inflammation, with elevated ALT levels, and potential hepatic decompensation [15, 16]. It is at this point when the viral DNA levels of HBV begin to decline, as does the presence of HBeAg. This is in large part due to the activated T-cell immune response, and subsequent destruction of infected hepatocytes [6]. An outcome of the immune clearance phase is HBeAg seroconversion, which has been found to be critical in predicting progression to cirrhosis and HCC.

Following HBeAg seroconversion, patients typically enter an “inactive carrier” phase, where HBeAg becomes undetectable, and HBe antibodies (anti-HBe) appear [17]. Typically the patient’s viral load is low or undetectable and ALT returns to normal. Biopsy at this time will show minimal fibrosis and mild hepatitis. If the patient had experienced severe liver injury during the “immune clearance” phase, cirrhosis can also be present [17].

During the “reactivation phase”, patients who were previously infected with HBV again have a detectable viral load, elevated ALT, and inflammation seen on biopsy [18]. In contrast to the “immune tolerant” phase, however, these patients do not have HBeAg positivity, but do have positive anti-HBe. As a result, this phase is known as the “HBeAg negative chronic hepatitis B” phase. As with the “immune clearance” phase, these patients can exhibit marked inflammation and hepatocyte destruction, and can experience hepatic decompensation during this phase.

The final phase of HBV infection is known as the “remission” or “inactive” phase, in which HBsAg may become negative, but anti-HBe and anti-HBc remain positive. Transaminases are normal at this time, and HBV viral loads are very low or undetectable.

**Figure 1.** Five phases of chronic hepatitis B *. * Adapted from Tong et al. (7) and modified by Halegoua-DeMarzio and Hann (8).
It is important to remember that once patients are infected, they remain positive for anti-HBc IgG throughout even after they lose HBsAg and after they acquire anti-HBs. Also, anti-HBe may often remain detectable.

Furthermore, as part of the infection of HBV into human hepatocytes, HBV DNA converts itself into a covalently closed circular DNA, known as cccDNA, inside the hepatocyte nucleus [19]. This cccDNA serves as a template for transcription of HBV viral mRNAs, which translate and produce HBV proteins as well as provide a template for HBV DNA synthesis [20]. Thus, although a patient’s viral load may be undetectable and HBsAg may become negative, the patient is not cured of HBV, as cccDNA will remain within hepatocytes.

3. Current treatments for chronic hepatitis B

Anti-HBV treatment drugs have made significant progress in improving the health and lifespan of patients with HBV. Beginning with interferon in 1991, therapies have become more targeted with lower resistance profiles and more tolerable side effects. The ultimate goal of hepatitis B treatment is to achieve remission, i.e., sustained suppression of viral replication. This, in turn, will lead to prevention of progression to cirrhosis and/or HCC. Several studies have demonstrated the reduction of HCC development with antiviral drugs [21–26].

Currently there are six approved treatments for HBV. The details of drugs and efficacy are shown in Table 1.

**Pegylated interferon alpha-2a.** The first treatment approved for HBV in 1991, pegylated interferon alpha-2a, or peg-IFN α-2a, is an immunomodulator, which also displays a weak effect against the virus itself [27]. It is administered as an injection, which patients receive weekly for a total treatment of 48 weeks. It has been shown to produce HBeAg seroconversion in 27% of patients, and 25% of patients develop an undetectable HBV DNA load [28]. It has been shown to have the best response for those individuals with genotype A with either ALT > 2x ULN or low HBV DNA, and for genotypes B and C with ALT > 2x ULN and low HBV DNA [29]. Although an effective treatment in the past, peg-IFN α-2a is a small percentage of current HBV treatments in the US [30]. Much of this is likely due to the requirement of an injection weekly, a large percentage of patients who fail to respond, and a significant side effect profile.

**Lamivudine.** The first nucleoside analogue approved for treatment of HBV, lamivudine (LMV) is a reverse transcriptase inhibitor. Functioning as a nucleoside analogue, it inhibits DNA synthesis of HBV. The treatment is extended across 1 year, and has been associated with a seroconversion rate of 16–18% at 1 year, and increases up to nearly 50% at 4 years [31, 32]. It is the least expensive of the nucleotide/nucleoside analogues, and is safe to use in pregnancy, which is one of its most common uses in current times. LMV has also been shown to reduce the rate of development of both fibrosis and HCC [33]. The most significant evidence of the effectiveness of LMV was shown in a randomized, controlled trial by Liaw et al., comparing LMV versus placebo in patients with chronic hepatitis B and high serum levels of HBV DNA.
[33]. The primary endpoint was progression of liver disease identified as either an increase in Child-Pugh score, bleeding from esophageal varices, or development of HCC. The study was discontinued early given that it demonstrated such a clear benefit of LMV compared to placebo [33]. Despite the success that has been shown with LMV, its use is limited, mainly due to the high incidence of resistance, especially compared with newer nucleotide/nucleoside analogues [34]. In one study, however, much lower resistance was observed if the baseline HBV DNA was < 10^6 copies/mL [35], and there has been an extensive review as to the discrepancies

<table>
<thead>
<tr>
<th>Name</th>
<th>Trade Name</th>
<th>Strong Points</th>
<th>Weak Points</th>
<th>Approved</th>
</tr>
</thead>
</table>
| Interferon alpha-2b and Pegylated Interferon 2a | Intron A Pegasys | -Finite duration of treatment  
- Durable response post-treatment  
- No known resistance | -Needle injection  
- High cost  
- 65-70% fail to respond  
- Significant side effects | 1991  
2005 |
| Lamivudine (LAM) | Epivir | -Oral  
- Safe with negligible side effects  
- Least expensive  
- Effective and safe in pregnancy | -Long term treatment is necessary  
- High incidence of resistance | 1998 |
| Adefovir Dipivoxil (ADV) | Hepsera | -Oral  
- Low resistance | -Long term treatment is necessary  
- Long term renal toxicity  
- Less potent than other treatments | 2002 |
| Entecavir (ETV) | Baraclude | -Oral  
- Potent viral suppression  
- Safe with negligible side effects  
- Low resistance | -Long term treatment is necessary  
- High cost | 2005 |
| Telbivudine (TLV) | Tyzeka | -Oral  
- Potent viral suppression  
- Effective and safe in pregnancy | -Long term treatment is necessary  
- High incidence of resistance | 2006 |
| Tenofovir (TDF) | Viread | -Oral  
- Most potent viral suppression  
- Safe with negligible side effects  
- No known resistance | -Associated with osteopenia  
- Long term treatment is necessary | 2008 |

*Adapted from Halegoua-De Marzio and Hann (8).

Table 1. Treatment options of chronic hepatitis B*. 

http://dx.doi.org/10.5772/66724
of LMV resistance among the multiple studies regarding the incidence of LMV resistance [36]. LMV also reduced vertical HBV transmission from highly viremic mothers to their newborns [37]. Currently, the use of oral antiviral agents during the first and second trimesters of pregnancy is not recommended.

**Adefovir dipivoxil.** The first nucleotide analogue, adefovir dipivoxil (ADV), was approved by the FDA for use in 2002. Similar to LMV in its mechanism of action, ADV functions as a reverse transcriptase inhibitor. As compared with LMV, however, ADV had both an increased antiviral potency, and an intrinsic stereoscopic structure that prevents emergence of viral resistance. HBe seroconversion was achieved in 12% of patients after 1 year of therapy with ADV, and a 53% rate of histological improvements in patients who were positive for HBeAg [38]. Of the patients who did seroconvert, it was found to be sustained in 91% of these patients [39]. Like LMV, however, prolonged use is associated with an increase in resistance, progressing from 3% at 2 years to 29% at 5 years [40]. Due to this, in addition to associated renal toxicity, the use of ADV has become increasingly rare with the development of newer, more effective therapies.

**Entecavir.** The second nucleoside analogue approved for treatment of chronic HBV, entecavir (ETV), was approved by the FDA for treatment in 2005. It has been shown to be superior at reducing HBV DNA levels, as compared with LMV [41]. In a phase 3 study comparing ETV to LMV after 1 year of treatment, patients were found to have improved virological response with HBV DNA < 400 copies/mL (67% vs 36%), improvement on histologic examination (72% vs 62%), and improvement in aminotransferases, namely ALT (78% returned to normal as compared to 70%) [41]. In longer term studies, up to 96% of patients had improvement in histologic examination, and improvement in fibrosis score after 6 years [42]. Improvements were even found in patients with cirrhosis. Entecavir also was shown to keep HBeAg-positive patients with HBV DNA levels below 300 copies/mL in 94% of patients at 5 years [43]. It has been shown to cause viral suppression quicker than ADV, and has been shown to significantly decrease the incidence of HCC in chronic HBV patients, with a 3.7% incidence in the ETV group as compared with 13.7% in the untreated group [23]. One of the most important features of entecavir, and a reason why it remains one of the two recommended treatments for chronic HBV today, is that it has a high genetic barrier and a very low incidence of resistance. The cumulative incidence of resistance after 6 years has been found to be 1.2% in nucleoside-naïve patients [44].

**Telbivudine.** Another nucleoside analogue similar in structure to LMV, telbivudine (TLV) was approved by the FDA for treatment of chronic HBV in 2006. In HBeAg-positive patients, the seroconversion with TLV was found to be 22% at 1 year and 30% at 2 years [45, 46]. Viral suppression to less than 300 copies of DNA/mL was found to be 60% after 1 year of TLV therapy, and 56% after two years of therapy [45, 46]. Unfortunately, although TLV was shown to have promising effects and to have a higher barrier to resistance than LMV, resistance has been found to be as high as 21.6% in HBeAg-positive patients, and 8.6% in HBeAg-negative patients [47]. Because of this, TLV currently is not a recommended first-line treatment. However, TLV is shown to be highly effective for those with low baseline HBV DNA and achieves undetectable HBV DNA at week 24. Therefore, TLV is highly effective for patients with the above
characteristics [48]. Furthermore, recent studies report the renoprotective effect of TLV, its role in preventing ADV-induced nephrotoxicity, and increased GFR improvement of renal function in liver transplant patients and in patients with compensated or decompensated HBV-related liver diseases [49–52]. The rate of vertical transmission was reduced when telbivudine was given to mothers with high viral loads during the third trimester of pregnancy [53]. Currently, the use of oral antiviral agents during the first and second trimesters of pregnancy is not recommended.

Tenofovir. The most recent nucleotide analogue, tenofovir disoproxil fumarate (TDF), was approved by the FDA for treatment of patients with chronic hepatitis B in 2008. Structurally similar but a more potent drug than ADV, TDF has been shown to produce more viral suppression in HBeAg-positive patients, with 76% of patients achieving viral loads < 400 copies/mL as compared with 13% of patients treated with ADV after 48 weeks of treatment [54]. ALT normalization, histologic improvement, and HBsAg loss were all also found to be significantly increased in patients treated with TDF as compared with ADV [54]. Data have shown an excellent continued response, with a 7-year viral suppression (HBV DNA levels < both 69 IU/mL and 29 IU/mL) of greater than 99% in both HBeAg-negative and HBeAg-positive patients [55]. In addition to its effectiveness, TDF has also been shown to have an extremely favorable resistance profile [56]. Due to the effectiveness and the virtual absence of resistance, TDF has been recommended as a first-line treatment in patients with chronic hepatitis B.

Several currently used guidelines are shown in Table 2.

Since the majority of chronic hepatitis B patients in the United States are immigrants from endemic countries, especially from Asia, where infection takes place commonly at birth or in early childhood, Asian-American algorithm is frequently used for treatment for this majority of HBV patients. These guidelines are as follows [7]:

1. For HBeAg (+) or (-) patient with chronic HBV with DNA > 10^4 copies/mL (> 2000 IU/mL) and ALT > ULN, treatment should be started with a first-line agent (ETV or TDF).

2. For cirrhotic patients with detectable HBV DNA, treatment should be started with ETV or TDF.

3. In HBeAg (-) patients with HBV DNA > 10^4 copies/mL (> 2000 IU/mL) and normal ALT, a liver biopsy is recommended. If not available, further stratification for risk factors (albumin ≤ 3.5 g/dL or platelets ≤ 130,000/μL, HCC first degree relative, age ≥ 40, male gender, ALT > 30 U/L for male and 19 U/L for female) should be conducted prior to treatment.

4. Monitoring treatment: Test for serum ALT every 3 months. Measure HBV DNA every 3 months until negative, then every 3–6 months. Measure HBeAg every 6 months until negative, then test for anti-HBe.

5. After seroconversion from HBeAg-positive to anti-HBe, test for HBsAg every 12 months. In HBeAg (-) patients, test for HBsAg every 12 months after sustained suppression of HBV DNA.

7. Surveillance for HCC with Alpha-fetoprotein (AFP) and abdominal ultrasound should be performed every 6 months in HBsAg-positive patients with chronic hepatitis, cirrhosis, and for patients with a family history of HCC.

8. With regard to stopping treatment, for HBeAg (+) patients, following HBeAg seroconversion, continue consolidation for 1–2 years before stopping therapy. However, the relapse rate is high, and longer consolidation therapy may be needed. For HBeAg (-) patients, antiviral therapy should be indefinite therapy until HBsAg seroconversion.

Before the antiviral drugs became available, 25–40% of HBV-infected individuals used to progress from chronic hepatitis to cirrhosis and eventually to HCC as shown in Table 3.

Table 2. Current treatments for hepatitis B in chronic hepatitis, as recommended by different guidelines (ref. 7, 69–72).

<table>
<thead>
<tr>
<th>Guidelines (last updated)</th>
<th>HBeAg (+) HBV DNA (IU/ml)</th>
<th>ALT (U/L)</th>
<th>HBeAg (-) HBV DNA (IU/ml)</th>
<th>ALT (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASL (2012)</td>
<td>&gt; 2,000</td>
<td>&gt; ULN</td>
<td>&gt; 2,000</td>
<td>&gt; ULN</td>
</tr>
<tr>
<td>US Algorithm (2015)</td>
<td>&gt; 20,000</td>
<td>&gt; ULN* or (+) biopsy</td>
<td>&gt; 2,000</td>
<td>&gt; ULN</td>
</tr>
<tr>
<td>APASL (4) (2016)</td>
<td>&gt; 20,000</td>
<td>&gt; ULN</td>
<td>&gt; 2,000</td>
<td>&gt; 2x ULN</td>
</tr>
<tr>
<td>AASLD (5) (2016)</td>
<td>&gt; 20,000</td>
<td>&gt; 2x ULN* or (+) biopsy</td>
<td>&gt; 2,000</td>
<td>&gt; 2x ULN</td>
</tr>
<tr>
<td>Asian American Algorithm (2011)</td>
<td>&gt; 2,000</td>
<td>&gt; ULN</td>
<td>&gt; 2,000</td>
<td>&gt; ULN</td>
</tr>
</tbody>
</table>

*EASL (European Association for the Study for the Liver) (72), US Algorithm (73), APASL (Asian Pacific Association of the Study of the Liver) (74), AASLD (American Association of the Study of Liver Diseases) (75), Asian American Algorithm (77).
ULN = Upper limit of normal; NS = Not stated.
* UNL: 30 IU/mL for men, 19 IU/mL for women
2000 IU/mL = 10^4 copies/mL
20,000 IU/mL = 10^5 copies/mL

Table 2. Current treatments for hepatitis B in chronic hepatitis, as recommended by different guidelines (ref. 7, 69–72).
In their 13-year follow-up study of HBV-infected carriers, Chen et al. have noted that higher baseline viral loads were associated with an increased rate of HCC [5] (Figure 2).

During the last 10 years, several studies have demonstrated that antiviral treatment significantly reduced the incidence of HCC [21–26]. However, all these treatment modalities are to suppress HBV replication. They do not fully eradicate the virus. The inability to eradicate HBV still leaves infected individuals at the risk for HCC. Current anti-HBV treatment can achieve “functional cure” but not “complete cure”, the terminology as coined by Zeisel et al. [19]. (Table 4).

### Table 3. Natural history of chronic hepatitis B infection.

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Chronic Hepatitis</th>
<th>Cirrhosis</th>
<th>Liver Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological</td>
<td>HBsAg → HBV DNA</td>
<td>Anti-HBs</td>
<td>Anti-HBe</td>
</tr>
<tr>
<td>Liver</td>
<td>Replication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Months → Years → Decades</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Higher baseline viral loads are associated with increased rate of HCC. *From Chen, et al. (5).*

In their 13-year follow-up study of HBV-infected carriers, Chen et al. have noted that higher baseline viral loads were associated with an increased rate of HCC [5] (Figure 2).

During the last 10 years, several studies have demonstrated that antiviral treatment significantly reduced the incidence of HCC [21–26]. However, all these treatment modalities are to suppress HBV replication. They do not fully eradicate the virus. The inability to eradicate HBV still leaves infected individuals at the risk for HCC. Current anti-HBV treatment can achieve “functional cure” but not “complete cure”, the terminology as coined by Zeisel et al. [19]. (Table 4).
4. Hepatocarcinogenesis

The pathogenesis for HBV-related HCC is not fully understood, but is likely multifactorial. HBV DNA level is a known factor, and the presence of HBV DNA has been shown to have a linear relationship to the development of HCC [5]. A high viral load leads to a persistent immune response against hepatocytes, with persistent inflammation, regeneration, and fibrosis. This up-regulated state of inflammation can in turn predispose to a malignant transformation [57]. Several studies have also suggested that the integration of HBV DNA into the host DNA can lead to chromosomal instability and eventual gene rearrangement. These rearrangements can, in effect, lead to deregulation and instability of gene expression, subsequently leading to oncogenesis [58–60].

The association with chronic HBV and HCC has been described as early as the 1970s. The landmark cohort study by Beasley et al. in 1981, which studied over 22,000 men in Taiwan, showed a significant association between chronic HBV carriers and the development of HCC. In this study, the relative risk of development of HCC in men with chronic HBV was determined to be 63 times higher as compared with uninfected individuals [61]. This study also designated the HBV vaccine (plasma vaccine by Blumberg and Millman followed by the recombinant vaccine) as the first “Cancer Vaccine” by the World Health Organization. The increased risk of HCC in patients with HBV has repeatedly been confirmed with smaller, more recent studies. Although HBsAg seroconversion and viral suppression are typically associated with protection against HCC, patients who have cleared their viral load have still been found to acquire HCC. This is likely due to the continued presence of cccDNA, in a mechanism that is not well understood. Studies have also shown that HCC development is better associated with patients who have had active HBV infection for longer time periods, including patients who were infected at younger ages. Thus, it is thought that HCC progression is likely a result of HBV replication itself and subsequent liver injuries that follow [62]. It also raises the point that in individuals infected earlier, carcinogenic processes may have already been in play prior to the halt of viral replication later in life, and the ability of HBV to integrate into the infected host’s hepatocyte genome is one of the most important direct pro-oncogenic properties.

In addition to chronic HBV carrier status, other risk factors have been identified which predispose patients with hepatitis B to HCC. These factors include co-infection with hepatitis C (HCV), a family history of prior HCC, concurrent alcohol use, and a predominance of genotype C [63–66]. Additionally, the presence of core promoter mutations, the most common of which is the HBx protein, a potent activator of multiple genes, including oncogenes, has been discovered [67].

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>Viremia</th>
<th>cccDNA</th>
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<tbody>
<tr>
<td>Functional cure</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Complete cure</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

*Ab, antibodies; cccDNA, covalently closed circular DNA
Adapted and edited from Zeisel et al. (19)
5. Future treatments

Most current guidelines recommend against HBV treatment of patients in the immune tolerant phase (Table 2). However, recent reports have indicated evidence that immune reactivity is in fact present in patients during this immune tolerant stage [68–70]. There is a growing opinion that to prevent HCC, we should consider earlier treatment of chronic hepatitis B as lucidly reasoned by Zoulim and Mason [71]. Given the emergence of HCC even in patients who had become seronegative, these guidelines should be readdressed in order to treat patients starting at a younger age, in order to prevent progression of disease and the development of HCC, as viral suppression alone has not proven effective for the absolute prevention of HCC. Additionally, the required long-term therapy imposes not only financial burden but may also put patients at risk for potential drug resistance and unknown toxicity.

Along with nucleoside/nucleotide analogues, treatment may need to include targeting the cccDNA and inhibiting viral entry into the newly formed hepatocytes. This may be accomplished via a T-cell vaccine which specifically targets HBV, enhancing innate immunity with toll-like receptor agonist. Several compounds have been identified which have the

<table>
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<tr>
<th>Targets</th>
<th>Compounds</th>
<th>Stage of development</th>
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<tr>
<td><strong>DAAs</strong></td>
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<td>HBV capsid</td>
<td>Phenylpropanamide derivatives</td>
<td>Preclinical and early clinical phase</td>
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<td>Heteroaroyl dihydroxypyrimidines</td>
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<td>rcDNA-cccDNA conversion</td>
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<td>NTCP</td>
<td>HIV preS1-derived lipopeptide</td>
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<td>Host factors involved in HBV</td>
<td>Iminosugar derivatives of butyloxyquinolymycin and related glycolipids</td>
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<tr>
<td>secretion and budding</td>
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<td>benzimidazole derivative</td>
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<tr>
<td>IFN-α</td>
<td>Phase I/II for HCC</td>
<td></td>
</tr>
<tr>
<td>PD1 blockade</td>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td><strong>Adaptive immune responses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-S-Core proteins (antigen-based vaccine)</td>
<td>GS-4774 in phase II</td>
<td></td>
</tr>
<tr>
<td>HBV DNA (DNA-based vaccine)</td>
<td>DV-601 in phase I</td>
<td></td>
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<tr>
<td></td>
<td>DNA vaccine pCMV52.5 in phase I/II</td>
<td></td>
</tr>
</tbody>
</table>

*cccDNA, covalently closed circular DNA; DAA, direct-acting antiviral; FDA, US Food and Drug Administration; HCC, hepatocellular carcinoma; HTA, host-targeting agent; IFN, interferon; LTβR, lymphoxygen-β receptor; NTCP, sodium taurocholate co-transporting polypeptide

Adapted and edited from Zeisel et al. (19)

Table 5. Emerging drugs against HBV.
potential for eradicating the virus. The clinical trials are in progress at different phases to further investigate these compounds [19]. Among these are direct-acting antagonists against the HBV capsid, against the HBV cccDNA, and against the HBV RNA. While the targets enhancing the innate immunity are mainly in the preclinical phase, they pose exciting possibilities for the future of HBV treatment. The potential drugs in the pipelines are shown below [19] (Table 5).

6. Conclusion

While there have been significant advancements in the understanding and management of hepatitis B virus, there remains much to be learned. The molecular mechanism and the subsequent carcinogenesis and progression of chronic HBV carriers to HCC remain in large part poorly understood. While significant improvements in treatment of HBV continue to be made, research toward HBV complete cure and the treatment landscape now is much different than it was at the end of the twentieth century. The development of nucleotide and nucleoside analogues, particularly entecavir and tenofovir, has significantly improved the ability of chronic HBV carriers to remain with undetectable viral levels. There remains, however, the possibility of development of HCC, in part likely in the early stages of infection, as well as the viral incorporation into hepatocyte DNA. Therefore, more effective treatment regimens need to be developed, and the prospect of treating individuals at earlier stages of HBV should be addressed. With multiple new therapies in the pipeline, the future of treating hepatitis B is an exciting and developing one, and hopefully, it will soon become a disease of the past.

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