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Review Article

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Short Review on Hepatitis B

Shaveta Sharma*, Chirag Chugh, Peeyush Kaushik, Upendra. K. Jain

Chandigarh College of Pharmacy, Landran, Mohali, Punjab

Abstract Hepatitis B virus currently infects more than 400 million people worldwide. The epidemiology of Hepatitis b virus infection is geographical diverse with population .Exploring the burden of chronic HBV infection this paper present a complete life cycle and biology of Hepatitis b virus in human body along with the symptoms of Hepatitis .it also illustrates the various modes of diagnosis. It includes primary treatment goals for patients with Hepatitis B (HBV) infection are to prevent progression of the disease, particularly to cirrhosis with the history of treatment. The approved therapy and combinations which are proved to be most effective and the development of resistance in body against the drugs and conclusion.

Keywords Actinomycetes, antiserum, *Erwinia spp.*, Isolation, *Ornithogalum spp*

Introduction

Hepatitis B

Hepatitis B is a potentially serious form of liver inflammation due to infection by the Hepatitis B virus (HBV).
It occurs in both rapidly developing (acute) and long-lasting (chronic) forms, and is one of the most common chronic infectious diseases worldwide. An effective vaccine is available that will prevent the disease in those who are later seen. More than 300 million persons throughout the world are infected by HBV. While most who become chronic carriers of the virus live in Asia and Africa, there are no fewer than 1.5 million carriers in the United States. Because carriers represent constant threat of transmitting the infection, the risk of Hepatitis B is always highest where there are many carriers. Such areas are said to be endemic for Hepatitis B. When infants or young children living in an endemic area are infected, their chance of becoming a chronic Hepatitis B carrier is at least 90%.
Hepatitis B virus (HBV) infection remains a global challenge, with one-third of the world's population having serological evidence of current or previous infection. Around 400 million people worldwide are chronically infected with HBV that leads to approximately 1 million deaths annually due to cirrhosis and hepatocellular carcinoma. Primary prevention by immunization remains the most effective way to control the spread of HBV especially in developing country. However, it is estimated that every year at least 27 million children worldwide do not receive the basic package of immunizations. About 25 % of children under five years' mortality is due to infectious diseases preventable by vaccine. Hepatitis B is a worldwide healthcare problem, especially in developing areas. An estimated one third of the global population has been infected with the Hepatitis B virus (HBV). Approximately 350-400 million people have lifelong chronic infection, and 0.5 % spontaneously seroconvert annually from having the Hepatitis B surface antigen (HBsAg) to having the Hepatitis B surface antibody (anti-HBs) [1].

Pathophysiology

Hepatitis B virus (HBV) is a hepadnavirus with the virion consisting of a 42-nm spherical, double-shelled particle composed of small spheres and rods and with an average width of 22 nm. It is an exceedingly resistant virus,

capable of withstanding extreme temperatures and humidity. HBV can survive when stored for 15 years at –20°C, [2].

Viral genome

The viral genome of Hepatitis B consists of a partially double-stranded, circular DNA molecule of 3.2 kilobase (kb) pairs that encodes the following 4 overlapping open reading frames:

S (the surface, or envelope, gene): Encodes the pre-S1, pre-S2, and S proteins.

C (the core gene): Encodes the core nucleocapsid protein and the e antigen; an upstream region for the S (pre-S) and C (pre-C) genes has been found

X (the X gene): Encodes the X protein

P (the polymerase gene): Encodes a large protein promoting priming ribonucleic acid (RNA)−dependent and DNA-dependent DNA polymerase and ribonuclease H (RNase H) activities

Core gene -The core antigen, HBcAg, is the protein that encloses the viral DNA. It can also be expressed on the surface of the hepatocytes, initiating a cellular immune response.

X gene - The role of the X gene is to encode proteins that act as transcriptional transactivators that aid viral replication. Evidence strongly suggests that these transactivators may be involved in carcinogenesis [3].

Antibody Production: The immunoglobulin M (IgM) subtype of anti-HBc is indicative of acute infection or reactivation, whereas the IgG subtype is indicative of chronic infection. The activity of the disease cannot be understood using this marker alone, however [4].

Antibody to HBeAg may be suggestive of a nonreplicative state if there is undetectable HBV DNA or the emergence of the core/precore variants and of chronic HBV HBeAg-negative disease [5].

Variants of HBV: With the newest polymerase chain reaction (PCR) assay techniques, scientists are able to identify variations in the HBV genome (variants).

The prevalence of the HBeAg-negative virus varies from one region to another. Estimates indicate that among patients with chronic HBV infection, 50-60 % of those from Southern Europe, the Middle East, Asia, and Africa, as well as 10-30% of patients in the United States and Europe, have been infected with this strain [6].

Immune Response: The pathogenesis and clinical manifestations of Hepatitis B infection are due to the interaction of the virus and the host immune system. The immune system attacks HBV and causes liver injury, the result of an immunologic reaction when activated $CD4^+$ and $CD8^+$ lymphocytes recognize various HBV-derived peptides on the surface of the hepatocytes. The final state of HBV disease is cirrhosis. With or without cirrhosis, however, patients with HBV infection are likely to develop hepatocellular carcinoma (HCC) [7].

Virus life cycle

The 5 stages that have been identified in the viral life cycle of Hepatitis B infection are briefly discussed below.

Stage 1: Immune tolerance

This stage, which lasts approximately 2-4 weeks in healthy adults, represents the incubation period. For newborns, the duration of this period is often decades. Active viral replication is known to continue despite little or no elevation in the aminotransferase levels and no symptoms of illness

Stage 2: Immune system active

In the immune active stage, also known as the immune clearance stage, an inflammatory reaction with a cytopathic effect occurs. HBeAg can be identified in the sera, and a decline in the levels of HBV DNA is seen in some patients who are clearing the infection. The duration of this stage for patients with acute infection is approximately 3-4 weeks (symptomatic period). For patients with chronic infection, 10 years or more may elapse before cirrhosis develops, immune clearance takes place, HCC develops, or the chronic HBeAg-negative variant emerges.

Stage 3: Inactive chronic stage

In the third stage, the inactive chronic infection stage, the host can target the infected hepatocytes and HBV. Viral replication is low or no longer measurable in the serum, and anti-HBe can be detected. Aminotransferase levels are within the reference range. It is most likely at this stage that an integration of the viral genome into the host's hepatocyte genome takes place. HBsAg still is present in the serum.

Stage 4: Chronic Disease

The emergence of chronic HBeAg-negative disease can occur from the inactive chronic infection stage (stage 3) or directly from the immune active/clearance stage (stage 2).

Stage 5: Recovery
In the fifth stage, the virus cannot be detected in the blood by DNA or HBsAg assays, and antibodies to various viral antigens have been produced. The image below depicts the serologic course of HBV infection [8].

Signs and Symptoms
The pathogenesis and clinical manifestations of Hepatitis B are due to the interaction of the virus and the host immune system, which lead to liver injury and, potentially, cirrhosis and hepatocellular carcinoma. Patients can have either an acute symptomatic disease or an asymptomatic disease.
Icteric Hepatitis is associated with a prodromal period, during which a serum sickness–like syndrome can occur. The symptomatology is more constitutional and includes the following:

- Anorexia
- Nausea
- Vomiting
- Low-grade fever
- Myalgia
- Fatigability
- Disordered gustatory acuity and smell sensations (aversion to food and cigarettes)
- Right upper quadrant and epigastric pain (intermittent, mild to moderate)

Patients with fulminant and subfulminant Hepatitis may present with the following:

- Hepatic encephalopathy
- Somnolence
- Disturbances in sleep pattern
- Mental confusion
- Coma
- Ascites
- Gastrointestinal bleeding [9]

Diagnosis:
Liver biopsy, percutaneous or laparoscopic, is the standard procedure to assess the severity of disease in patients with features of chronic active liver disease (i.e., abnormal aminotransferase levels and detectable levels of HBV DNA) [10].
HBV Infectivity in real life
Intravenous Inoculation - Comparisons of the chimpanzee infectious doses and the number of HBV DNA molecules in HBeAg positive plasmas showed that ten or less virus particles are sufficient to start a readily detectable HBV infection if they are *injected intravenously*. These findings are confirmed by observations on the very rare inadvertent transmissions of HBV from blood donors in the early phase of infection when HBsAg and even HBV DNA are not yet detectable by the most sensitive techniques.
In normal life, small wounds and intimate mucocutaneous contact may allow transmission from a highly viremic person to others. Epidemiological experience shows that this danger is high when the values exceed 10^7 viruses/mL plasma, but it is nearly non-existent when lower than 10^5/ml [11].

Treatment & Management
Approach Consideration
In general, for HBeAg-positive patients with evidence of chronic HBV disease, treatment is advised when the HBV DNA level is at or above 20,000 IU/mL (10^5 copies/mL) (or, per the EASL, >2,000 IU/mL and when serum alanine aminotransferase (ALT) is elevated for 3-6 months. The NIH also indicates that immediate therapy is not routinely indicated for patients who have the following:
Chronic Hepatitis B with high levels of serum HBV DNA but normal serum ALT levels or little activity on liver biopsy (immune-tolerant phase)
Low levels of or no detectable serum HBV DNA and normal serum ALT levels (inactive chronically infected/low replicative phase)
Positive serum HBV DNA but not HBsAg (latent HBV infection), unless the patient is undergoing immunosuppression [12].

Background

More than 400 million people are chronically infected with Hepatitis B virus (HBV) worldwide. While the majority of the infected individuals live in the Asia Pacific region, at least 1.25 million live in the United States. The reported prevalence rate of chronic Hepatitis B (CHB) is limited by the fact that epidemiological studies do not include the prison population or taking into consideration the continuous influx of immigrants to the United States from endemic areas with a high prevalence rate of chronic HBV infection. Screening programmes conducted in Asian American immigrant populations in San Francisco and New York City have shown that approximately 10–15% of newly tested persons have chronic HBV infection, leading to a revised estimate that 2 million people in the United States have chronic HBV infection [13].

Up to 40% of patients with CHB will eventually develop complications of liver failure, either from decompensation of cirrhosis or acute exacerbation of CHB, or the development of hepatocellular carcinoma (HCC). Prolonged replicative phase, elevated HBV DNA levels, infection with Hepatitis C, Hepatitis D or HIV and concurrent alcohol use are some of the factors associated with disease progression to cirrhosis in patients with chronic Hepatitis B. The risk of developing HCC and cirrhosis has been shown to be related to the level of serum HBV DNA (Figure 1). Such complications result in poor quality of life, reduced life expectancy, and impose substantial demands on the healthcare resources [14].

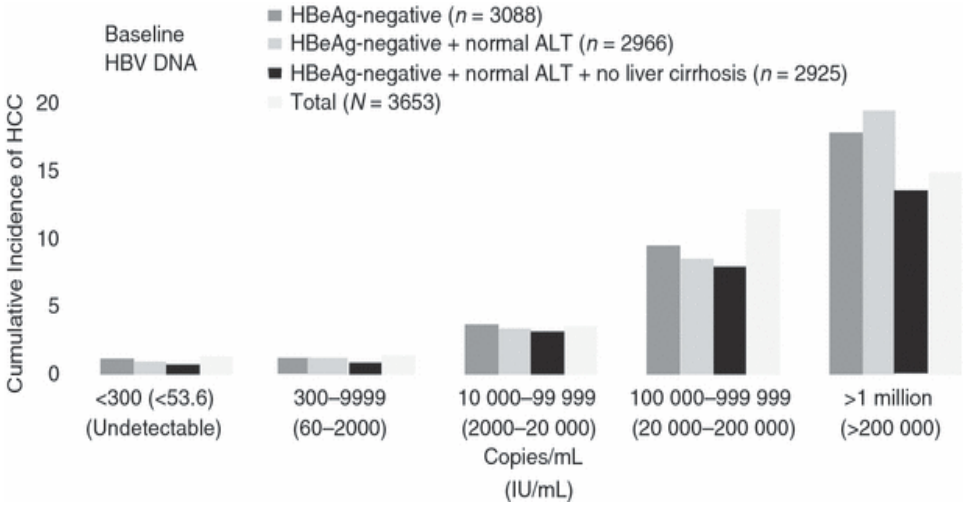

Figure 1 [14]

Prevention is the best approach to the ultimate control of HBV infection. Universal HBV vaccination programmes in children have resulted in a significant decrease in the incidence of Hepatitis B in the vaccinated population. In the United States, universal vaccination was instituted in 1991. Analysis of the National Health and Nutritional Survey (NHANES) data from 1988 to 1994 vs. data from 1999 to 2006 revealed a decreased prevalence of HBV infection from 5.4% to 4.7% respectively. The difference in prevalence was more significant in the 6 to 19-year-old group (1.9% vs. 0.6%), supporting the positive impact of universal vaccination in decreasing the burden of CHB. Although vaccination results in a decrease in the number of new cases of HBV infection, it has no impact on pre-existing CHB. Patients with CHB rely on currently approved anti-therapy to achieve optimal virological suppression [15].

Natural History

The age of acquisition of HBV infection has a major impact on the natural history of CHB. While 90% of individuals infected at birth or in early childhood develop CHB, more than 95% of patients infected as adults clear the virus. The hallmark of acute HBV infection is elevated alanine aminotransferase (ALT) levels, the presence of Hepatitis B surface antigen (HBsAg), IgM antibody to Hepatitis B core antigen (anti-HBc) and Hepatitis B e antigen (HBeAg), although the latter serological test is not routinely used in practice.

Once infected with HBV, an individual will either clear the virus or enter the four phases of chronic HBV infection: immune tolerance, immune clearance, seroconversion to inactive carrier and reactivation. The immune tolerance phase is seen in individuals infected at birth or early in life, but is short-lived or not apparent in those infected in adulthood. The immune tolerance phase is characterised by high levels of viral replication (elevated HBV DNA levels and presence of HBeAg), but normal ALT levels. Histological features of this phase include presence of minimal or absence of inflammation and fibrosis on histological examination. However, a liver biopsy is seldom done in this stage [16].

The immune clearance phase follows the immune tolerance phase. It signals clearance of infected hepatocytes and results in elevated or fluctuating ALT levels and persistently high HBV DNA levels. If a liver biopsy is performed, inflammation with varying degrees of fibrosis is usually present. However, cirrhosis may be seen in individuals who have repetitive Hepatitis flares and prolonged duration of this phase. Seroconversion and development of antibodies to HBeAg (anti-HBe) usually occurs in this phase. Seroconversion occurs at an annual rate of 5–15% without therapy, but this process can be hastened by initiation of antiviral therapy.

HBV genotype also has an impact on progression of chronic Hepatitis B. Individuals with genotype A, B, D or F typically clear HBeAg at <20 years of age, whereas individuals with genotype C clear HBeAg at a mean of 47.8 years. In addition, individuals with genotype C have an increased likelihood of having persistently detectable serum HBeAg and a longer time to spontaneous HBeAg clearance compared with those with genotypes A, B, D and F. Those with genotypes C and F are also more likely to revert to the HBeAg-positive state after losing HBeAg.

The nonreplicative phase of chronic HBV infections follows the immune clearance phase once seroconversion from HBeAg to anti-HBe occurs. It is characterised by normal ALT levels, undetectable or low levels of serum HBV DNA and the presence of anti-HBe. Individuals in this phase are referred to as inactive HBsAg carriers. Absence of or minimal inflammation with varying degrees of fibrosis can be seen on liver biopsy in this phase. Some inactive carriers may also seroconvert to antibody to HBsAg (anti-HBs). Despite the development of anti-HBs, a small amount of serum HBV DNA can often be detected using sensitive polymerase chain reaction techniques in such inactive carriers. Recent studies have shown that inactive HBsAg carriers have a substantial risk of HCC and liver-related death compared with those not infected with HBV.

Treatment of chronic Hepatitis B

The paradigm of treatment of CHB continues to evolve as newer data from studies on the natural history of CHB emerge. Analysis of longitudinal studies is challenging the current indications for initiation of Hepatitis B treatment, as well as the endpoints of therapy [17-23]. Analysis of a large cohort of Asians patients revealed a significantly increased risk of development of long-term complications in subjects with ALT level 1–2 times the upper limit of normal (ULN) compared with patients with ALT levels >2–6 ULN. Many studies have also demonstrated that over two-thirds of patients with long-term complications of CHB have previously achieved HBeAg seroconversion. Rather than achieving HBeAg seroconversion, complete suppression of the HBV DNA might be a better suitable endpoint. HBsAg seroconversion might be the ideal endpoint, but it is only achieved in small proportion of patients regardless of therapy. In addition, HBsAg seroconversion does not protect against development of HCC in the setting of cirrhosis.

The importance of monitoring individuals with low-serum HBV DNA and normal ALT levels regardless of their HBeAg status has also become recognized in recent years. Serial ALT and HBV DNA monitoring every 3 months for 1 year after the initial diagnosis and again 6–12 months thereafter is usually recommended to detect intermittent flares of Hepatitis B. Treatment should be initiated regardless of the level of viraemia if active inflammation is also detected on liver biopsy. In the case of HBeAg negative CHB, treatment is continued lifelong to prevent relapse. Therefore, achieving maximum viral suppression without the development of antiviral drug resistance, reducing progression to cirrhosis and decreasing the risk of developing HCC are the primary treatment endpoints. However, in a natural history study of predominantly Asian Americans, a substantial proportion of patients who developed HCC or died from non-HCC-related liver complications would have been excluded from treatment based on existing guidelines.

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Dietary Limitation

Patients with acute or chronic Hepatitis without cirrhosis have no dietary restrictions. For individuals with decompensated cirrhosis (signs of portal hypertension or encephalopathy), the following dietary limitations are indicated:

A low-sodium diet (1.5 g/day)

High-protein diet (ie, white-meat protein, such as chicken, turkey, or fish)
Fluid restriction (1.5 L/day) in cases of hyponatremia.

Approved therapy for Hepatitis B

Seven drugs are approved for treatment of CHB by the FDA: interferon alfa-2b, peginterferon alfa-2a, lamivudine, adefovir, entecavir, telbivudine and tenofovir. An interferon-based therapy offers a fixed duration of therapy, but it is limited by its substantial side effects and poor tolerability in some individuals. Oral nucleoside/nucleotide therapy may lead to the emergence of antiviral drug resistance with prolonged use. Selection of the appropriate therapy requires taking into account any prior agent used to treat CHB and assessment for the potential of cross resistance. Resistance to lamivudine will negatively affect the potency and efficacy of entecavir and telbivudine, and has been documented to be as high as 75% after 5 years of therapy. Given its low genetic barrier to resistance, lamivudine is no longer used as first-line agent. Similarly, telbivudine use is dependent on achieving undetectable HBV DNA by week 24 of therapy. Individuals who do not achieve this milestone at week 24 have an overall 22% rate of telbivudine resistance in HBeAg-positive patients, and 9% in HBeAg-negative patients. Once this milestone is achieved, continued viral suppression persisted through week 96 of therapy in the pivotal trial.

Antiviral Medication includes

Lamivudine: Lamivudine is an analogue of cytidine. It can inhibit both types of HIV reverse transcriptase and also the reverse transcriptase of Hepatitis B virus. It is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated [18].

Adefovir: Adefovir works by blocking reverse transcriptase, an enzyme crucial for the HBV to reproduce in the body. It is approved for the treatment of chronic Hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (primarily ALT) or histological active disease.

The main benefit of adefovir over lamivudine (the first NRTI approved for the treatment of HBV) is that it takes a much longer period of time for the virus to develop resistance to it. Lamivudine or adefovir, and less likely to cause resistance [19].

Telbivudine: Telbivudine is an antiviral drug used in the treatment of Hepatitis B infection. It is marketed by Swiss pharmaceutical company Novartis . Clinical trials have shown it to be significantly more effective than lamivudine [20].

Baraclude: Baraculde (entecavir) is an antiviral medication. Entecavir prevents certain virus cells from multiplying in your body.Baraclude is used to treat chronic Hepatitis b virus (HBV) in adults and children who are at least 2 years old.

Sofosbuvir: Sofosbuvir is a substrate of P-glycoprotein, a transporter protein that pumps drugs and other substances from intestinal epithelium cells back into the gut. Therefore, inducers of intestinal P-glycoprotein, such as rifampicin and St. John's wort, could reduce the absorption of sofosbuvir.

Mechanism of Action: Sofosbuvir inhibits the Hepatitis C NS5B protein. Sofosbuvir appears to have a high barrier to the development of resistance. Sofosbuvir is a prodrug. It is metabolized to the active antiviral agent GS-461203 (2'-deoxy-2'-α-fluoro-β-*C*-methyluridine-5'-triphosphate). GS-461203 serves as a defective substrate for the NS5B protein, which is the viral RNA polymerase, thus acts as an inhibitor of viral RNA synthesis. Although sofosbuvir has a 3' hydroxyl group to act as a nucleophile for an incoming NTP, a similar nucleotide analogue, 2'-deoxy-2'-α-fluoro-β-C-methylcytidine, is proposed to act as a chain terminator because the 2' methyl group of the nucleotide analogue causes a steric clash with an incoming NTP [23]. Sobosbuvir would act in a similar way [21].

Interferon alfa-2b (Intron A): Interferon is the drug of choice for treating several chronic forms of viral Hepatitis, including Hepatitis B and C. This drug is approved around the world for the treatment of chronic Hepatitis C, chronic Hepatitis B, hairy cell leukemia, chronic myelogenous leukemia, multiple myeloma, follicular lymphoma, carcinoid tumor, and malignant melanoma.

Peginteferon alfa-2a: Peginterferon alfa-2a has replaced standard interferon alfa-2b due to improved pharmacokinetic properties, a less demanding injection schedule, a more convenient dosing regimen and comparable or improved efficacy. Pegylated interferon still results in the highest rate of off-treatment sustained response after 1 year of therapy. Forty-eight weeks of therapy with Peginterferon alfa-2a results in a 27% rate of HBeAg seroconversion and 25 % rate of loss of HBV DNA. Six months after discontinuation of therapy, the HBeAg seroconversion rates increased to 32 %. Loss of HBsAg with the appearance of anti-HBs occurred in 4–6% of

patients after 1 year of treatment and 6 months of post-treatment follow-up. Even after discontinuation of interferon therapy, 12–65% of patients lost HBsAg within 5 years of HBeAg loss. Achieving early virological response, defined as >2$\log_{10}$ drop in serum HBV DNA or suppression to levels below 10^5 copies/mL in the first 2 weeks of therapy, is associated with induction of long-term remission after stopping therapy. The addition of lamivudine to peginterferon alfa-2a therapy has no effect on serological response rates in HBeAg-positive and HBeAg-negative CHB, but results in more vigorous suppression of the HBV DNA during treatment in patients who received combination therapy [22].

Management of Resistance: Nucleoside and nucleotide analogues can be divided into three groups based on their barrier to resistance. Lamivudine has a low genetic barrier to resistance, adefovir and telbivudine have an intermediate barrier to resistance and entecavir and tenofovir have high genetic barrier to resistance. The oral agents suppress but do not eradicate the HBV. Therefore, most patients will require long-term treatment to maintain the HBV DNA suppression. Prolonged treatment is associated with increasing risk of development of resistance, especially when a nucleos(t)ide with low genetic barrier is used as monotherapy.

Reported anti-viral resistance in Hepatitis B treatment-naïve patients according to published trial results. The trials were not head-to-head comparisons and used HBV assays of different sensitivities.

The terminology defining viral resistance continues to evolve. Virological breakthrough (VBT) or secondary treatment failure is the first manifestation of drug resistance and may precede biochemical breakthrough. VBT is defined as an increase in serum HBV DNA >1 $\log_{10}$ (10-fold) from nadir or re-detection of HBV DNA at levels ≥10-fold the lower limit of detection of the HBV DNA assay after having undetectable test result before. Confirmed VBT refers to persistence of VBT 1–3 months from the initial detection time, with or without further increase in HBV DNA. Genotypic resistance is universally defined by the detection of viral populations bearing amino acid substitutions in the reverse transcriptase region of the HBV genome that have been shown to confer resistance to antiviral drugs in *in vitro* phenotypic assay.

Monotherapy with agents having low genetic barriers has been associated with rapid development of resistance, as is the case with lamivudine and adefovir. Entecavir and tenofovir are the only two approved drugs for treatment of CHB with a high genetic barrier to resistance. They are considered now as first-line agents in the treatment of CHB. The combination of a nucleoside and nucleotide analogue has the theoretical advantage of offering synergistic viral suppression and a higher genetic barrier to resistance formation. However, a de novo approach has not been studied. The addition of peginterferon to adefovir or lamivudine had the only advantage of lowering the rate of viral resistance, but did not result in higher sustained response rates. It will be important to learn whether the use of tenofovir or entecavir in addition to PEG-IFN will lead to a higher sustained response rate [23].

Conclusion

The goal of treatment of CHB is to achieve continuous viral suppression leading to a decrease necro-inflammation, improvement in the stage of fibrosis and prevention of progression to cirrhosis, liver failure and HCC. Prolonged treatment of patients resulting in viral suppression has been proven to prevent disease progression and improve clinical outcomes. Therefore, use of agents with a high genetic barrier to resistance as first-line of therapy is vital to improving outcomes in patients with CHB. Peginterferon, tenofovir and entecavir are the only approved agents with a high genetic barrier to resistance. However, achieving viral suppression is also dependant on patient adherence in taking the medication, as up to 20% of the patients report taking <80% of their oral Hepatitis B medication over a 1-year study period. Achievement of viral suppression is not completely protective against development of hepatocellular carcinoma. Studies have shown that even inactive HBsAg carriers or patients who lose HBsAg as a result of treatment remain at an increased risk of developing HCC.

Different strategies are needed to decrease the risk of HCC and progression of fibrosis to cirrhosis. Such studies may provide new insights leading to a change in the current understanding of initiation or stopping therapy. Such studies might clarify whether early suppression of the HBV virus in the replicative phase may lead to decreased rate of HCC or change the course of chronic Hepatitis B. In addition, it remains to be discovered whether de-novo combination therapy with two agents with high genetic barrier in treatment-naïve patients will change the natural course of chronic Hepatitis B.

Finally, HBV infection cannot be completely eradicated due to the continued presence of the cccDNA in the nucleus of the infected hepatocytes, but it can be prevented by advocating strategies for universal vaccination of newborns and high-risk individuals and by increasing the awareness of the global burden of Hepatitis B [24].

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