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REVIEW ARTICLE

Clinical Profile, Genotype and Management Updates of *Hepatitis B Virus*

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Abstract *Hepatitis B virus* (HBV) is a well known agent of acute and chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. Around 400 million people worldwide carrier of HBV of which more than 250 million reside in Asia, and 1–2 million people have died from it. It has a partially double-stranded DNA, having 3.2-kb genome size and replicate via reverse transcription of RNA intermediate. In the natural history or during the antiviral therapy of chronic HBV infection, seroconversion from HBeAg to anti-HBeAg is usually accompanied by a decrease in viral replication and remission of liver disease. Based on genomic sequence data HBV is classified into eight genotypes A–H and four major serotypes ayw, ayr, adw and adr on the basis of complete genome and S gene sequence analysis. Genotypes and serotypes are useful tools in understanding the epidemiology of HBV infection. HBV genotypes have distinct geographical distributions. The HBV variants appear during HBeAg seroconversion and they bring mutations in the precore region (PC) that prevent HBeAg synthesis. Another common HBeAg variant is the basal core promoter mutant (BCP) characterized by point mutation in the promoter of both HBeAg mRNA and core protein mRNA. The most frequent core promoter mutation is the double A1762T and G1764A nucleotide exchange, which results in a substantial decrease in HBeAg expression but enhanced viral genome replication. The approved antiviral drugs such as Interferon, lamivudine, adefovir dipivoxil, entecavir and telbivudine for purpose of treating chronic HBV infection is to prevent or stop the progression of liver injury by suppressing viral replication or eliminating infection. Sustained losses of viral markers of active viral replication (HBeAg and HBV DNA) are the standard end point of the therapies.

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Introduction

Hepatitis B virus (HBV) is partially double stranded DNA virus which belongs to the *Hepadnaviridae* family and has been classified as the member of the genus *Orthohepadnavirus*. HBV is a major causative agent of acute hepatitis, chronic hepatitis, liver cirrhosis and hepatocellular carcinoma in Asians, African and Southern European countries, with an estimated 350–400 million carrier around the world and 1–2 million people have died from it. In India the prevalence rate of hepatitis varies from 1 to 13 percent; with an average of 4.7% [28]. HBV genotypes are classified into eight genotype A–H and are geographically distributed [49]. In India predominantly genotype A and D are found, genotype D is more predominant over A [17, 59] (Fig. 1). The presence of Hepatitis Be antigen (HBeAg) in the serum is used as a serological marker that correlates with the presence of viral replication with occurring liver damage. As HBeAg disappears from the serum, antibody to HBeAg (anti-HBe) becomes detectable. The appearance of anti-HBeAg in the blood stream indicates biochemical and histological improvement of the liver injury with decreased viral detection. Two major groups of mutation result in reduced or blocked HBeAg expression, the first is precore stop codon mutation (translational mechanism) and the second is core promoter mutation (transcriptional).The precore stop codon mutation (TGG→TAG) at codon 28 of

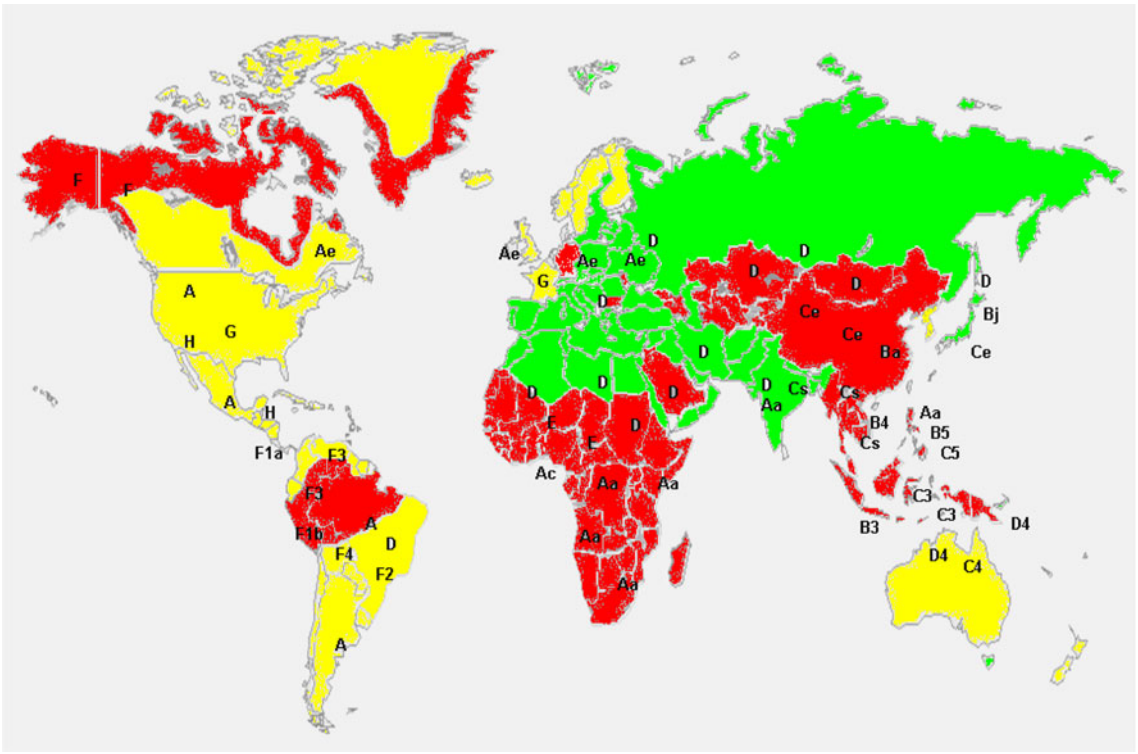

Fig. 1 Geographic distibution of *Hepatitis B virus* genotype and subgenotype. Regions with high, intermediate and low endemicity are shown by ■, ▭ and ■, respectively. A, B, C, D, E, F, G, and H represents the genotype with subgenotype Aa, Ac, Ae/B1, B2, B3, B4, B5, Bj/C1, C2, C3, C4, C5/D1, D2, D3, D4. (Color figure online)

the precore/core gene, is a mutation that occurs in the nucleotide position of 1896, substituting guanine with adenine [7]. The second is core promoter mutations (A1762G1764→T1762A1764) located within (codon 15) which results in a substantial decrease in HBeAg expression but enhanced viral genome replication [54]. There are several antiviral agents such as interferon, peg-interferon, lamivudine, telbivudine, adefovir and entecavir which have been approved for the treatment of hepatitis B. Several types of vaccines are also available for controlling the HBV infection. In the present article we review the currently available information related to molecular biology, pathobiology, epidemiology, prevalence and mode of transmission of HBV infection and current strategies for controlling the HBV infection including approved therapeutic intervention.

Molecular Biology

The family of *hepadnaviridae* comprises members recovered from a variety of animal species including the woodchuck hepatitis virus (WHV), the ground squirrel hepatitis virus (GSHV), and the duck HBV. Common features of all of these viruses are enveloped virions containing 3–3.3 kb of relaxed circular, partially duplex DNA and virion associated DNA-dependent polymerases that can repair the gap in the virion DNA template and have reverse transcriptase activities. The HBV is a 42 nm partially double stranded DNA virus, composed of a 27 nm nucleocapsid core (HBcAg), surrounded by an outer lipoprotein coat(also called envelop-HBeAg) containing the surface antigen (HBsAg) [22, 46, 47]. Electron microscopy gives the initial views of the hepatitis B genome. In virions the genome appears to be circular and partially double stranded. The genome is approximately 3200 nucleotides in length but does not abide by the usual classification criteria of viruses [44]. Numbering of base pairs of the HBV genome is based on the cleavage site for the restriction enzyme *Eco*RI or at homologous site, if *Eco*RI site is absent. However, other methods of numbering are also used based on the start codon of the core protein or on the first base of the RNA pregenome. There are at least seven major subtypes of HBV, distinguished by differences in the surface antigen gene [16]. There are four defined overlapping open reading frames (ORFs) i.e., several genes overlap and use the same DNA to encode viral proteins (Fig. 2). The four genes are core, surface, X and polymerase. The core gene encodes the core nucleocapsid protein (important in viral packing) and hepatitis B envelop antigen (HBeAg). The surface gene encodes pre-S1, pre-S2 and S protein (yielding large, middle and small surface

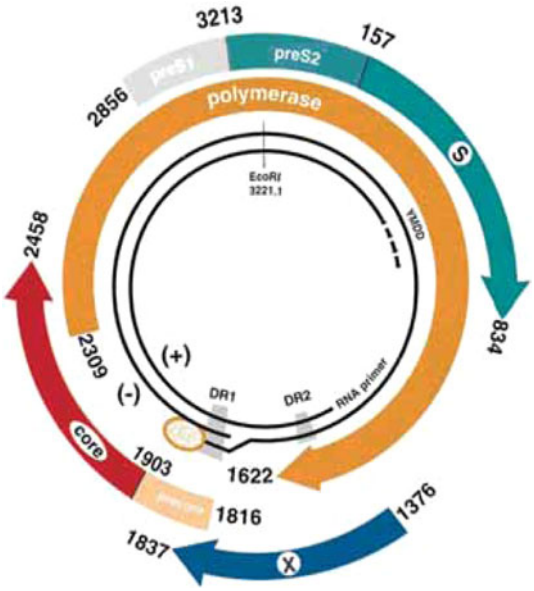

Fig. 2 Organization of the HBV genome. The nucleotide numbering of the genome is based on the unique *Eco*RI restriction enzyme site shown. The different open reading frames encoded by the genome, designated as S, core, polymerase, and X, are indicated by the *arrows*. Nucleotide numbers designate the boundaries of each ORF with position 1 mapped at the *Eco*RI site. Shown also are the map positions for the viral direct repeats (DR1 and DR2) and the approximate position of the YMDD locus in the HBV polymerase gene. Abbreviations: *S* surface antigen; *Y* tyrosine; *M* methionine; *D* aspartate; *prec* precore; *DR* direct repeat segment, used in viral replication

proteins, respectively). The X gene encodes the X protein, which has transactivating properties and may be important in hepatic carcinogenesis. The polymerase gene encodes a large protein with functions critical for packaging and DNA replication including priming, RNA and DNA dependent DNA polymerases and RNAse activities [6]. Although HBV is a DNA virus, replication is thought an RNA-replicative intermediate requiring an active viral reverse transcriptase/polymerase enzyme. The reverse transcriptase for both HBV and immunodeficiency virus is believed to lack proofreading function that is common in other polymerase. There fore exhibite the mutation rate more than 10-fold higher than other DNA viruses, the estimated mutation rate is approximately one nucleotide/10,000 bases/infection year [20].

Path Biology

Hepatitis B virus primarily interferes with the functions of the liver by replicating in the liver cells known as hepatocytes. The receptor is not yet known, though there is evidence that the receptor in the closely related duck HBV is corbaxypeptides D [19, 25]. Infected hepatocytes are characteristically enlarged and their cytoplasm has a ground glass appearance. HBsAg is found associated with the endoplasmic reticulum; core particles containing HBcAg are present in the cell nuclei. HBV virions (DANE particle) bind to the host cell via the pre-S domain of the viral surface antigen and are subsequently internalized by endocytosis. Pre-S and IgA receptors are accused of this interaction. HBV pre-S receptors are primarily expressed on hepatocytes; however, viral DNA and proteins have also been detected in extrahepatic sites, suggesting that cellular receptors for HBV may also exist on extrahepatic cells. During HBV infection the host immune response does not play a significant role in this process, the adaptive immune response, particularly virus specific cytotoxic T lymphocytes (CTLs), contributes to most of the liver injury associated with HBV infection. By killing infected cells and by producing antiviral cytokines capable of purging HBV from viable hepatocytes, CTLs eliminate the virus [24]. Although liver damage is initiated and mediated by the CTLs, antigen-nonspecific inflammatory cells can worsen CTLs -induced immunopathology and platelets activated at the site of infection may facilitate the accumulation of CTLs in the liver [34].

Clinical Phases of Hepatitis B Infection

HBV Carrier

Patients with HBsAg positivity for more than 6 months are termed as chronic HBsAg carriers. This designation should be reserved, however, for patients with the clinically 'asymptomatic' or 'healthy' HBsAg carrier stated as specified. The natural course oh chronic HBV can vary greatly with a broad spectrum of clinical, biochemical, serological and histological presentations [34]. In principle, chronic HBsAg carriers can be divided into two groups, those with evidence of chronic liver disease and those without chronic liver disease. The first group is defined as chronic hepatitis B; and the second as asymptomatic or healthy HBsAg carrier state. For practical purposes, the distinction between the two groups may be based on the presence of elevated ALT/AST levels. Patients with chronic hepatitis B may be clinically symptomatic or asymptomatic, healthy carriers are by definition asymptomatic [23].

Acute Hepatitis B Infection

Acute HBV infection has a mean incubation period of 90 days (range 30–180 days). Hepatitis B can not easily be clinically differentiated from other infectious and noninfectious causes of hepatic injury. The clinical course may

be mild or severe and associated with jaundice. Almost in all cases, significant elevations of the serum transaminases (ALT/AST) occur. The diagnosis of acute HBV infection is most reliably made by the presence of IgM antibody to HBV core antigen (IgM anti-HBc) which appears a few weeks following HBV surface antigenemia (HBsAg). Although IgM anti-HBc is rapidly superseded by IgG anti-HBc, IgM may persist for months to years and may even reappear during flares of chronic HBV. In self-limiting infection in the immunocompetent host, the appearance of antibody to the HBsAg (anti-HBs) marks the recovery from infection. This generally appears weeks to months following disappearance of serum HBsAg. HBeAg and HBV DNA are markers of active viral replication in hepatocytes; if these markers are present early in the course of acute infection, they may also persist in the chronically infected individual.

Chronic Hepatitis B Infection

Chronic hepatitis means active on going inflammation of liver persisting for more than 6 months, which is detectable by biochemical and histological examinations. The biochemical hallmark of chronic hepatitis is an increased ALT/AST with minimal elevation of alkaline phosphates. Chronic hepatitis B is serologically defined as HBsAg positivity for greater than 6 months. There are two forms of chronic hepatitis B: first is chronic persistent hepatitis (CPH) and second one is chronic active hepatitis (CAH), both forms are characterized by hepatic inflammation with concomitant reparative changes and fibrosis. Chronic infection is frequently asymptomatic, occasionally hepatomegaly, splenomegaly, transient episodes of jaundice and persistent elevation of transaminases are seen. Serologically chronic HBV infection is characterized by HBsAg +ve, HBeAg +ve, HBV-DNA +ve, anti-HBc +ve and anti-HBsAg −ve (Table 1). Chronic hepatitis may be divided into two phases, a replicative phase and non-replicative phase. The replicative phase is characterized by the presence of HBeAg and HBV DNA in serum, by the presence of HBcAg in hepatocytes as assessed by immunohistochemistry, by high infectivity and accompanying liver injury. The non replicative phase is characterized by absence of the above markers of HBV replication, the absence of HBcAg in hepatocytes, limiting infectivity and usual minimal liver injury. In this phase HBV DNA detectable in the liver is often integrated into the cellular genome. Patients in the replicative phase tend to have more severe chronic hepatitis, while those in the non-replicative phase tend to have minimal or mild chronic hepatitis or remain asymptomatic hepatitis B carrier. Replicative HBeAg positive HBV infection may be associated with normal ALT/AST levels and normal liver histology; non-replicative HBV infection may be associated with sever chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC) development [40].

Hepatocellular Carcinoma (HCC)

The development of hepatocellular carcinoma and liver failure are main causes of death from chronic hepatitis B, various factors involving the host and the virus may contribute to the development of cellular carcinoma. It is estimated that over 500,000 people die each year from the consequence of HBV infection [41]. Chronically infected subjects have a 100 times increased risk of hepatocellular carcinoma with non-carriers [62]. A recent study suggested that patients with positive HBsAg have the risk of developing HCC by 10 fold than normal, and with HBeAg positivity have increased risk by 60 folds [52]. The additional use of alcohol, consumption of aflotoxin in diet and confection with HCV or HDV are independent factors for HCC in HBV infected patients. Unlike hepatitis C, development of HCC in hepatitis B patients does not require preceding cirrhosis.

Fulminant Hepatitis

This is defined as the development of acute liver cell injury proceeding to liver failure and hepatic encephalopathy

Table 1 Serological response to HBV infection

Stage of infection	HBsAg	Anti-HBs	IgG-anti-HBc	IgM	HBeAg	Anti-HBe
Incubation	+	−	−	−	+/−	−
Acute hepatitis B	+	−	+	+	+	−
HBsAg-negative acute HepB	−	−	+	−	−	−
Healthy HBsAg carrier	+	−	+	+/−	−	+
Chronic hepatitis B	+	−	+	+/−	+	−
Convalescent HBV infection	−	+	+	+/−	−	+
HBV vaccination	−	+	−	−	−	−

Note: + Present (reactive), − Absent (non reactive)

within 8 weeks in a patient without any known previous liver disease. Clinically the patient deteriorates with development of deep jaundice, confusion and drowsiness. The encephalopathy can progress into deep coma, because of massive liver necrosis. There is deficiency of clotting factors; hence the PT/INR is always increased. At this stage mortality is greater than 50% unless a liver transplant can be performed. Death may occur from infection, hypoglycemia, and increased intracranial pressure with cerebral edema or renal failure. Massive hepatic necrosis with architectural collapse is seen histologically despite this if regeneration occurs, histological recovery is the rule. Fulminant hepatitis develops in about 1% of cases [45]. Patients infected with pre-core mutants often manifest severe chronic hepatitis, early progression with cirrhosis and variable response to interferon therapy, it may have an association with fulminant hepatic failure [64]. Genetic heterogeneity of HBV, co infection or super infection with other viral hepatitis agents or host immunological factors may be associated with the development of fulminant hepatitis B [45, 63]. A rapid fall in ALT and AST in patients with fulminant hepatic failure may be erroneously interpreted as a resolving hepatic infection when in fact hepatocytes are being lost and outcome is fatal [22].

Epidemiology

HBV infection is a global public health problem. Approximately two billion people in the world have been actually infected by HBV and there are nearly 350 million people chronically infected with HBV [33]. At least 15–25% of chronically HBV infected people will die due to liver disease caused by HBV. The significance and the magnitude of the problem vary from country to country. The developed countries of Northern Europe and America have considerably controlled the infection by means of effective vaccination and improved sanitation, particularly measures taken for transfusion safety. HBV infection is less than 1% in population of these countries and contributes to only 5–10% chronic liver disease in these countries. The situation is just contrast in the developing countries of Asia and Africa, particularly those of Far East and South Africa. In these countries, HBV infection occurs in 5–10% of the general population and is responsible for more than 50% of chronic liver disease, constituting a public health priority. In India, HBV infection is of intermediate endemicity, with nearly 4% of the population being chronic HBV carriers, i.e., about 40 million people [57].

In 1995 the population of India was reported to be around 900 million, and the average estimated carrier rate of HBV was 4%, placing India in the intermediate range for hepatitis B endemicity and giving an approximate total of 36 million carriers. Among the estimated 400 million HBsAg carriers world wide, therefore, India alone contributes 9% of the total. There are wide variations in social, economic and health factors in different regions of India, which may explain the differences in HBV carrier rates reported by investigators in different parts of the country i.e., 5–8%. A study from Delhi reported blood transfusion hepatitis in 7% of recipients and 20% of cases were due to HBV infection and in Lucknow the prevalence of HBV was found about 2% in general population [52].

The higher rate of chronic HBV infection among commercial sex workers (23.3%) is of concern, particularly in a country with an estimated 4.58 million persons infected with HIV. A meta-analysis showed significant heterogenecity and they have analyzing the non tribal and tribal population separately, shown a significant heterogenecity among the studies. Almost all the studies have analyzed a crass sectional studies and therefore indicative of the point prevalence of the disease. The true prevalence in the non tribal population was 2.4% and was 15.9% in the tribal population [3]. Of the HBV genotypes, HBV/A and HBV/D have been reported from different parts of the India [8, 12, 59]. India is a vast country having a long history of population influx from different countries resulting in different patterns of chronic disease in different parts [51].

Any one who has not been immunized can get HBV. Small children and adolescents are particularly vulnerable. Children contract the disease from their mother at birth or simply from another child while playing. Though children rarely develop acute illness after infection, children run the highest risk of developing chronic hepatitis B which may cause liver complication later in life.

Mode of Transmission

As a viral disease, hepatitis B is transmitted from person to person through blood, saliva, vaginal fluids and most other body fluids. It is usually transmitted by contact with blood and body fluids in the following ways: as during birth from mother to baby, through infected needles during injection with unsterilized needles or syringe containing HBV from an infected person (i.e., from another patient or recycled needles), sexually transmitted through sexual intercourse because of contact with blood or other body fluids, social contacts with transmission between children during playing, through cuts, scrapes and scratches.

The predominant route of transmission among children is horizontal during the preschool and early school years [56]. Hepatitis B virus is not spread by air, food or water and is not transmitted through breast feeding, tears, sweat, and urine, stool and droplet nuclei.

Diagnosis

Diagnosis of hepatitis is made by biochemical assessment of liver function. Initial laboratory evaluation should include: total and direct bilirubin, ALT, AST, alkaline phosphates, prothrombin time, total protein, albumin, globulin, complete blood count and coagulation studies [45]. Diagnosis is confirmed by demonstration in sera of specific antigen or antibody. Three clinical useful antigen/antibody systems have been identified for hepatitis B: Hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs), HBV e antigen (HBeAg) and antibody to HBeg (anti-HBe), HBV core antigen (HBcAg).

HBsAg can be detected in the serum from several weeks before onset of symptoms to months after onset. HBsAg is present in serum during acute infections and persist in chronic infections. The presence of HBsAg indicates that person is potentially infectious [19]. Presence of HBeAg is associated with relatively high infectivity and severity of disease. Demonstration of anti-HBc in serum indicates HBV infection current or past. IgM anti-HBc is present in high titer during acute infection and usually disappears within 6 months, although it can persist in some cases of chronic hepatitis, this test may therefore reliably diagnosed acute HBV infection. IgG ant-HBc generally remains detectable for a lifetime. Anti-HBe appears after anti-HBc and its presence correlates to a decreased infectivity. Anti-HBs replace HBsAg as the acute HBv infection resolving. Anti-HBs generally persist for a lifetime in over 80% of patients and indicate immunity [45, 63].

Treatment and Prevention Strategies

Vaccination

The recombinant genetically engineered hepatitis B vaccine has gained world wide acceptance. Its safety and protective efficacy has been established and it is now recommended all over the world. For children (1–12 years) receive 3 doses of 10 mg intramuscularly at 0, 1 and 6 months intervals. Older children and adults require 3 doses of 20 mg at the same intervals. This induced a protective antibody response in more than 95% infants, children and adolescents. Babies born to mothers who are HBsAg positive should receive active immunization soon after birth. Administration of hepatitis B immunoglobulin if available and feasible should be given within 12 h of birth. The preterm and low birth weight babies given the first dose soon after birth produce antibodies in the protective range. Bhave et al. [4] have shown that four dose schedule including a booster at 12 months is effective in low birth babies in India.

Conventional Therapy

The purpose of treating chronic HBV infection is to prevent or stop the progression of liver injury by suppressing viral replication or eliminating infection. Sustained losses of viral markers of active viral replication (HBeAg and HBV DNA) are the standard end point of the therapies [39]. In general, seroconversion from HBeAg to anti HBeAg is associated with the disappearance of HBV DNA in serum and remission of liver disease. However, some patients with anti-HBeAg continue to show signs of viral replication (i.e., have high level of HBV DNA) and have active liver disease [60]. These groups of patients were recently discovered to have a mutation in the precore region of the HBV genome which decreases or prevents the production of HBeAg [33]. The approved antiviral drugs such as Interferon, lamivudine, adefovir dipivoxil, entecavir and telbivudine have been found to be effective in treating HBV infection.

Interferon

Interferon-α belongs to a family of natural occurring proteins that have antiviral and immunomodulatory action [43]. In 1992, interferon-α2b was approved by the US Food and Drug Administration (FDA) for use in persons with chronic HBV infection.

The ideal patient for INF-α therapy has high ALT/AST and low HBV DNA levels,HbsAg +ve or anti Hbe and HBV DNA positivity, a short duration of disease and is negative for HDV and HIV [11]. The current recommended dose of interferon is 5 million U injected subcutaneously each day or 10 million U injected subcutaneously 3 times per week, for a period of 16 weeks result in seroconversion from replicative to non-replicative HBV infection in approximately 35% of patients with a concomitant improvement in liver histological features [37].

Nucleoside and Nucleotide Analogues

Nucleoside or nucleotide analogues compete with naturally occurring purines and pyrimidines for binding to HBV DNA polymerase. They require intracellular phosphorylation for their activity. Analogues lacking a 3′-OH group on the sugar moiety result in immediate chain termination. Many of these compounds are unnatural L-enantiomers [35]. One of the significant impacts of these oral agents is their beneficial effects on end stage liver disease. Unlike INF, nucleoside or nucleotide analogues are well tolerated by patients with decompensated liver disease and significant improvement of hepatic synthetic function has been documented [2].

Lamivudine

Lamivudine (Epivir-HBV, Glaxo Wellcome) is the first nucleoside analogue to be approved by the FDA (December 1998) for the use in chronic HBV infection [27]. Lamivudine is generally given in a dose of 100–300 mg daily. Lamivudine competitively inhibits viral reverse transcriptase and terminates proviral DNA chain extension [50]. Unlike interferon, lamivudine and other nucleoside analogues do not affect the host immune response. Lamivudine decreases HBV replication by approximately 3–4 log copies in most patients. It is rapidly absorbed after oral administration and is excreted largely unchanged by the kidneys [26]. Lamivudine induces a more rapid pattern of response than interferon: levels of HBV DNA showed a median reduction of 97% after 2 weeks and 98% by 1 year. Suppression of HBV DNA was well maintained during treatment [15]. In the Asian multicentre study, therapy was continued after 1 year and resulted in continued improvement in the liver necroinflammation. The sustained seroconversion rate of HBeAg to anti Hbe increased during the second year from 17 to 27%. However, the presence of detectable HBV DNA increased to 48% among lamivudine treated patients after 2 years of therapy, suggesting lamivudine resistance [38]. In other study after 1 year of treatment 45% of initially positive patients have lost HBV-DNA with normal ALT, but only 15% remain HBV-DNA negative 16 weeks after stopping the therapy [36]. Unfortunately, lamivudine therapy is followed by replication in 27% of patients at 1 year, and 58% after 2 years of treatment and 65% after 5 years [10]. This resistance is marked by amino acid mutations in a highly conserved YMDD (tyrosine, methionine, aspartate, aspartate) motif of the active sites of the polymerase. These mutants impair HBV replication, but the virus is still pathogenic [32].

Adefovir

Adefovir is an adenine nucleotide analogue with broad-spectrum activity [13]. It is the oral prodrug of an acyclic nucleotide monophosphate analogue as adefovir dipivoxil. It can inhibit both the reverse transcriptase and DNA polymerase activity and is incorporated into viral DNA causing chain termination [9]. Dose of adefovir dipivoxil is 30 mg/day for 4 weeks. Toxicity of adefovir includes renal insufficiency and frequent development of hypophospataemia [55]. Adefovir 10 mg is associated also with a high rate of primary nonresponse in up to 30% of the patients with HbeAg positive chronic hepatitis B. Although, adefovir at 30 mg has higher antiviral potency, it is not recommended for its potential nephrotoxicity [42]. Clinical trials have suggested that adefovir may be effective as first line monotherapy for the treatment of chronic HBV infection [18]. In two phase II studies, 12 weeks of adefovir treatment at daily doses of 30 mg or greater resulted in a reduction of 4 log copies in levels of HBV DNA. Loss or seroconversion of HbeAg occurred in 20–27% of patients and 0% of controls [21]. No resistant mutations have been reported to date with adefovir. In vitro, lamivudine-resistant strains are generally susceptible to adefovir [61].

Entecavir

Entecavir is the newest and most potent nucleoside analogue to be licensed worldwide for the treatment of chronic hepatitis B infection. Entecavir is the third nucleoside analogue to be licensed for the treatment of chronic HBV infection. It is a deoxyguanosine analogue. Synthesis of the novel compound was first reported in 1997 [5]. It now takes its place amongst the other therapies available for chronic HBV infection, viz lamivudine, adefovir and interferon. In an early 28-day, randomized, placebo-controlled, dose escalating study in 42 patients all doses of entecavir used (0.05. 0.1, 0.5 and 1.0 mg) showed significant suppression of HBV replication by more than 2 log copies/ml [14]. The next study was a 24-week, randomized, double-blind, multicentre, phase II trial of 169 patients comparing safety and efficacy of three doses of entecavir (0.01, 0.1 and 0.5 mg/day) with lamivudine (100 mg/day). There was a significant dose-relationship in the entecavir treatment groups. Significantly more patients treated with 0.5 mg/day entecavir had undetectable HBV DNA. Unlike lamivudine, the absorption of entecavir is significantly affected by food; hence it should not be ingested within 2 h of a meal. There was no incidence of resistance to entecavir in the two treatment naïve trials. This is in contrast to 13 and 6% of patients in the HBeAg-positive and HBeAg-negative trials, respectively, developing resistance to lamivudine. However, in the lamivudine-refractory trial, two patients (1.4%) developed resistance to entecavir [30]. In vitro enzymatic studies showed that lamivudine resistance HBV polymerases have reduced susceptibility to entecavir. However, because of the high potency and efficient phosphorylation of entecavir, sufficient intracellular concentrations of active entecavir triphosphate are still being generated in cell cultures to effect potent inhibition of lamivudine resistance HBV [58].

Telbivudine

Telbivudine (LdT) is a novel agent for the treatment of CHB. It is an HBV-specific L-nucleoside analogue of thymidine. The chemical name of telbivudine is β-L-2-deoxythymidine. Telbivudine is an unsubstituted, unmodified β-L-2-nucleoside and the first compound of this series.

Telbivudine must be activated by phosphorylation and is efficiently metabolized to 5-riphosphate derivative. 5-triphosphate metabolite of β-L-2-deoxynucleosides interacts with the viral polymerase and inhibits viral replication and results in obligate chain termination of DNA synthesis [53].

In October 2006, Idenix announced the approval of telbivudine by the US Food and Drug Administration. First clinical study of telbivudine, safety, antiviral activity, and pharmacokinetics were assessed in 43 adults with HBeAg positive chronic hepatitis B. This placebo-controlled dose escalation trial investigated 6 telbivudine daily dosing levels (25, 50, 100, 200, 400, and 800 mg/day); treatment was given for 4 week, with a 12 week follow-up. The results indicate that telbivudine was well tolerated at all dosing levels, with no dose related or treatment-related clinical or laboratory adverse events. Marked dose related antiviral activity was evident, with a maximum of telbivudine doses of 400 mg/day or more. In the 800 mg/day cohort, the mean HBV DNA reduction was 3.75 log10 copies/ml at week 4, comprising a 99.98% reduction in serum viral load [29]. In both HBeAg-positive and HBeAg-negative patients, telbivudine had greater antiviral efficacy than did lamivudine. The mechanism underlying the effect of pretreatment HBeAg status on therapeutic and histologic response is uncertain, but it may derive from the lower baseline HBV DNA levels and high viral clearance rates observed in HBeAg-negative patients [31]. Telbivudine appears to be efficacious, easy to take with a good safety profile, proving to be a valuable therapeutic option in the management of hepatitis B [1].

Conclusion

Compared to the progress made in Western Countries, research in the Indian subcontinent is going on at a slow pace. In spite of the fact that HBV continues to be a major threat to the Indian population, mandatory blood screening is not rigorously implemented. The introduction of the mandatory screening of blood donors for HBsAg in India during the 1990 has resulted in marked decrease in post-transfusion of HBV infection [48]. Infection with HBV is unique and represents an enigma to the clinician for the simple reason that majority of the patients remain asymptomatic, with fluctuating liver enzyme levels. Thus, rather than developing novel therapeutic strategies, development of a vaccine to prevent the viral infection should be of paramount importance. To pursue further any advance research in the area of diagnosis, therapy or prevention, epidemiological data is the primary requirement. Conducting time to time such studies in different areas helps us to keep track of virus evolution too.

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