Review Article

Impact of Hepatitis B Virus Infection in Patients with Liver Transplantation

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Abstract | Hepatitis B virus (HBV) as a deadly viral pathogen and crucial challenge for mankind is directly involved in the progress of hepatocellular carcinoma (HCC) subsequently affecting 250 million human population. Due to the complex viral genome of HBV, complete recovery from hepatitis is not achieved. Epidemiologically, it has been classified into infectious and serum hepatitis. The pattern of disease progression manifests liver inflammation, chronic hepatitis and hepatocellular carcinoma. In this article, we present a comprehensive review characterizing the viral architecture, life cycle, infectivity mechanisms, immune escape strategies, disease epidemiology and preventive measures associated with HBV. The current antiviral therapeutics are not providing adequate protection against HBV. It is mandatory to characterize and devise novel antiviral therapies to control the spread of hepatitis

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Introduction

Hepatitis B is a severe liver disease condition that can affect every age of personals like babies and children, not just adults who engage in risky behaviors so it is very important to protect infants and young children from Hepatitis B as there is a greater probability than adults to develop serious chronic (long-term) infection that can result in liver damage and liver cancer [1]. Hepatitis B is one of the major challenge for mankind, it is estimated to cause about 800,000 deaths per year mostly that leads to liver cancer and cirrhosis. Primarily it is started from the infection that occurs in childhood endemic for the disease. Hepatitis B is mortality and morbidity problem and chronic carriers to spread the infection from child to child, and to susceptible subjects via sexual activity and unsafe medical procedures such as unsafe injections. In areas of lower endemicity the virus spreads mainly among young adults as a result of lifestyle or occupational exposures [2]. Most significantly, Hepatitis (inflammation of the liver) identified as an illness causing jaundice. However, it was unseen until World War II, on the basis of epidemiologic data, that there were two distinct types of hepatitis: epidemic or infectious hepatitis and serum hepatitis. Serum hepatitis, the history of the epidemiology of hepatitis B represents a landmark in the general understanding of viral infections, their outcomes and distribution [3].

Epidemiology

HBV prevalence as well as transmission patterns vary greatly throughout the world. Being highly prevalent

in Asia and sub-Saharan Africa as well as other parts of the developing countries (high-prevalence countries), western countries e.g. Western Europe and United States are so called low-prevalence countries

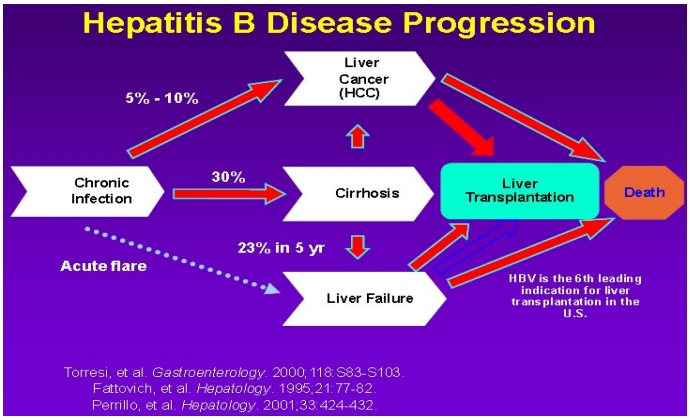

Figure 1: *Progression of Hepatitis B.*

[4]. While in high-prevalence countries HBV transmission usually occurs perinatal from chronically infected mothers, infection in low-prevalence countries predominately occurs horizontal during adolescence by sexual contacts or percutaneously by drug injection [5,6]. The risk of developing a chronic HBV infection is approximately 90% if HBV infection is acquired perinatal. Vertical perinatal HBV infection does not lead to the induction of a cellular immune response and a lifelong, persistent infection is established in most cases [5,7]. In contrast, up to 95% of immunocompetent adults spontaneously clear the infection [8,9]. Even though there is a safe and effective HBV vaccine available and national HBV vaccination programs have dramatically reduced the prevalence of HBV infection, chronic HBV infection is still a major health problem [7].

Table 1: *Epidemiology survey of hepatitis B virus infection in 1992.*

Region	Province	HBsAg (%)
North East	Heilongjiang, Jilin, Liaoning	10.71
North Central	Neimenggu, Beijing, Tianjin, Hebei, Shanxi	5.53
East	Shandong, Jiangsu, Shanghai, Zhejiang, Anhui, Jiangxi, Fujian	9.94
South Central	Henan, Hubei, Hunan, Guangdong, Guangxi	12.75
South West	Xizang, Sichuan, Yunnan, Guizhou	8.90
North West	Xinjiang, Gansu, Qinghai, Ningxia, Shangxi	8.68

HBV epidemiology in China

Infection with HBV and development of HCC are responsible for heavy disease burdens in China. In 2006, the Ministry of Health of China (MOH) estimated that, among Chinese aged 1 to 59 years as of 1992, the national prevalence of HBV infection and HBV carriers was 57.63% and 9.75%, respectively, which corresponded to 690 million infected people, 120 million carriers, and 20 million with chronic hepatitis (Table 1) [10]. The disease burden of HBV is very large, even when compared to that of tuberculosis, which was only responsible for 1.4 million new cases in 2000 [11]. Chronic hepatitis B (CHB) is one of the most serious infectious diseases in China. To date, the MOH has taken several measures to address HBV. In its National Plan for Prevention and Treatment against Hepatitis B for 2006-2010, the MOH stated that CHB causes serious consequences for patients, their families, and society as a whole and that it is a major cause of poverty and a health issue of the highest priority. The prevalence of HBV infection in China is one of the highest in the world. In addition, China has the highest incidence of HCC (37.9 and 14.2 for males and females, respectively, per 100,000 world standard 340,000 cases), with 630,000 newly diagnosed cases in 2002 [12].

In China, HBV is the most important risk factor for the development of HCC. Although the HBV immunization program is expected to greatly reduce HCC incidence, a few more decades are required before an obvious decrease among the general population will be seen. With the high cost of the current antiviral therapy for CHB, HCC control among existing carriers depends on reducing risk factors that accelerate the development of HCC among carriers. Since the introduction of HBV immunization, control of HBV infection. HBsAg, hepatitis B surface antigen has been substantially progressing in China, which will lead to a dramatic decrease in the disease burden from HBV infection and HCC [13]. Therefore, understanding the role of immune cells in chronic HBV infection will become more and more important.

Structure and molecular virology

The hepatitis B Virus is a small non-cytopathic, parenterally transmitted, enveloped hepadnaviridae virus with circular, partially double-stranded DNA and represents the medically important prototype of enveloped DNA viruses [14]. The longer, negative

DNA strand is the coding strand for viral mRNA and viral pregenomic RNA transcription. The shorter, plus strand is variable in length and includes two direct repeats (DR1 and DR2) at its 5' end, required for strand-specific DNA synthesis during replication. At the 5' end of both strands a short cohesive overlap region stabilizes the circular structure of the genome. Liver-specific expression of viral gene products is conferred by two enhancer elements, En1 and En2 [15, 16, 17].

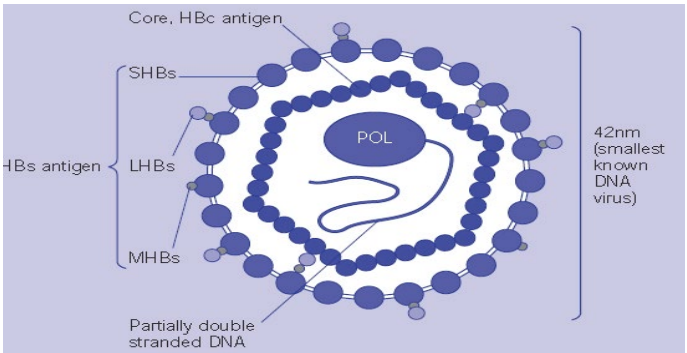

Figure 2: *Prototype of enveloped DNA viruses.*

The HBV genome is approximately 3200 bp in length and contains four overlapping open reading frames (ORFs). Each ORF encodes for specific structural proteins: The S gene, which can be structurally and functionally divided into the pre-S1/L-, pre-S2/M- and Surface/S region, encodes for the viral surface envelope proteins, HBsAg. Three in-frame start codons within the ORF are responsible for production of the different surface proteins. The L- and the M-protein share the amino acids (aa) of the S-domain and are extended by 55 (M-protein) or 108/119 (L-protein) amino acids, called pre-S2 or pre-S1 [14]. The precore/core gene encodes for the nucleocapsid protein HBcAg and the secreted, non-structural precore protein, HBeAg. Multiple in-frame translation initiation sites in both the S and the C gene can give rise to related but functionally distinct proteins. The polymerase ORF encodes for the viral polymerase, which is functionally divided into three domains: the terminal protein domain involved in encapsulation and initiation of minus-strand synthesis, the reverse transcriptase domain responsible for genome synthesis and the ribonuclease H (RNase H) domain which degrades pregenomic RNA and initiates replication. The fourth ORF encodes for HBxAg, a protein with multiple functions. HBx is known to be involved in signal transduction, transcriptional activation, DNA repair and protein degradation inhibition. Furthermore, it is known that HBx is required for viral replication as well as productive HBV propagation [4, 17, 6, 18]. Today eight HBV genotypes (A-H) – going along with differences in clinical outcome – are known. The genotypes have different geographic distributions.

Life cycle

The HBV life cycle has been studied in great detail; however, the hepatocyte- specific preS1 receptor, responsible for specific and probably irreversible binding of the virus to a hepatocyte remains unknown. Due to the strong liver tropism of HBV, replication exclusively takes place in hepatocytes. The initial phase of HBV infection is the reversible and non-cell-type specific attachment to cell-associated heparan sulfate proteoglycans, followed by the irreversible binding of the pre-S1 domain in the L-protein to and so far, unknown preS1-receptor [14, 19].

Two different virus entry pathways have been proposed: (i) endocytosis followed by the release of nucleocapsids from endocytic vesicles; (ii) fusion of the viral envelope with the plasma membrane. The direct mechanism has not been elucidated so far. The released nucleocapsid is transported to the nucleus, more precisely to the nuclear core complex along microtubules [20, 19, 6]. After the release of the partially double stranded, relaxed circular viral DNA (rcDNA) into the nucleoplasm, the plus strand of the rcDNA is completed by the viral polymerase. Viral polymerase and RNA primers used for plus-strand synthesis are finally removed by cellular enzymes. The formation of the cccDNA (covalently closed circular DNA) is achieved by covalent ligation of both strands. The cccDNA molecule is organized as a chromatin-like structure (mini chromosome) and seems to be regulated by host specific factors, however, it is not amplified during mitosis but has the potential to persist in host cells for several years [21, 19]). The host cellular transcription machinery is used by the cccDNA to produce viral RNAs necessary for viral protein production and viral replication. This process is regulated by both cellular and viral proteins, which may modulate viral gene expression by interacting with the promoters of the four viral ORFs. All four major mRNAs use a single common polyadenylation signal, however, processing of viral RNAs, nuclear export as well as stabilization seem to be exclusively mediated by host factors [22,19,6]). cccDNA transcripts, transcribed by cellular RNA polymerase II, are

intronless, 5'-end capped and polyadenylated. They are divided into two different species: subgenomic RNA (sgRNA) and pregenomic RNA (pgRNA), relevant for viral replication. While the pgRNA serves as a template for reverse transcription and mRNA of the viral core protein and the viral polymerase, the sgRNA directs the translation of the regulatory x protein and the three envelope proteins by free ribosomes. The three envelope proteins are directly synthesized into the membrane of the endoplasmic reticulum (ER). The pgRNA, in contrast, forms an encapsidised complex in the cytoplasm with the core protein and the polymerase, where it is transcribed into negative-strand DNA. rcDNA is then generated by plus-strand synthesis from the negative DNA strand. The viral nucleocapsids self-assemble via complex formation of the pgRNA with the core protein and the polymerase.

Nucleocapsids are either re-imported to the nucleus to generate new cccDNA or enveloped by the envelope proteins and exported via the ER and the Golgi complex. Two different groups of secreted particles are distinguished:
(i) Subviral envelope particles (SVPs; 22nm) without DNA-containing nucleocapsids.
(ii) Dane particles (infectious virions; 42nm) which are enveloped DNA-containing nucleocapsids. Naturally infected hepatocytes contain up to 50 or more copies of cccDNA [23, 17, 19, 6].

Hepatitis B virus infection

Acute and chronic HBV infection: Viral hepatitis is a necroinflammatory liver disease of variable severity. While 95% of immunocompetent adults usually suffer from a self-limiting, transient liver disease, 5% of adults and up to 90% of newborns are persistently infected with HBV. Persistent HBV infection is associated with chronic liver diseases and a high risk for the development of cirrhosis or HCC [24, 25, 26, 27]. Acute HBV infection can lead to anicteric, icteric or fulminant hepatitis, however about 60% of the patients show only a mild, asymptomatic and subclinical illness, which is not even detected. Acute fulminant hepatitis occurs only in 0.5% of patients and is characterized by signs of liver failure.

Phases of chronic HBV infection: One of the following four biochemical and serological profiles: may present in chronic HBV infectied patients (1) with normal HBeAg positive alanine ami- notransferase (ALT) levels; (2) with abnormal HBeAg positive ALT levels; (3) with normal HBeAg negative ALT levels; and (4) with abnormal HBeAg negative ALT levels. Infact these four kinds of presentation stand for different phases of chronic HBV infection.

Which leads to the dynamic interplay of composite interactions involving HBV, the hepatocyte and the host immune response, the natural track of chronic HBV infection consists of distinct phases, differentiated and diagnosed on the basis of HBeAg/anti-HBe serology, serum HBV DNA levels, ALT levels and liver histology. Naturally, chronic infection attained prenatally or during childhood consists of three chronological stages: start with the immune tolerance phase, followed by immune clearance phase, and to end with the low replicative inactive phase [28, 29, 30]. In a subset of immobile carriers, HBV may reactivate and generate immune mediated liver injuries. This reactivation phase can be observed as an alternative of immune clearance phase [2]. Few of the adult patients who progress to chronic hepatitis B, there is generally no or very short primary immune tolerance phase. Successful immune clearance happens more readily. Otherwise, the clinical path is the same as seen in prenatally attained infection.

Immune tolerance phase: The immune tolerance phase is described by the presence of HBeAg, very high serum level of HBV DNA (>2 × 107 IU/mL) and HBsAg (4.5–5.0 log10 IU/mL) [31, 32, 33], normal ALT level, normal liver or only minimal necro inflammatory activity and scant fibrosis. Immuno staining of HBV antigens in liver indicates that HBsAg is dispersed diffusely on the hepatocyte membrane and crucially in the cytoplasm, and hepatitis B core antigen (HBcAg) is distributed largely in nuclei [34]. Typically, there is slight or no disease progression as long as serum ALT levels remain normal and the immune tolerance is maintained [35].

The precise mechanisms for immune tolerance are unidentified. Although HBV virus does not cross the placenta, HBeAg secreted by the virus does. Experiments in mice propose that a transplacental transfer of maternal HBeAg may stimulate an exact unresponsiveness of helper T cells to HBeAg in neonates. Because HBeAg and HBcAg are highly cross-reactive at the T-cell level, deletion of the helper T-cell response to HBeAg results in an in effective cytotoxic T-lymphocyte (CTL) response to HBcAg, the main objective of the immune response [36].

The viral population recognized during the immune tolerance phase generally consists of entirely wild type HBeAg-positive HBV with little or no mutant type HBeAg-negative HBV [36, 37].

Immune clearance phase: The conversion from immune tolerance to immune clearance phase generally take place between age 20 and 40, but may sometimes begin prior and even arise in pediatric patients. During this phase, although serum HBeAg is still positive but ALT levels become abnormal, accompanied by reducing levels of serum HBV DNA and HBsAg. Serum HBV DNA levels normally go beyond 20,000 IU/mL and HBsAg levels are generally in the range of 3.5–4.5 log10 IU/mL [31, 32, 33]. There is a positive correlation between serum HBsAg levels and serum HBV DNA or intrahepatic covalently closed circular DNA (cccDNA) levels. Liver biopsy reveals modest or ruthless necro inflammation with uneven amounts of fibrosis. HBsAg is spreaded diffusely on the hepatocyte membrane and focally in the cytoplasm, as seen in immune tolerance phase, but intrahepatic nuclear HBcAg expression declines with concomitant boost in cytoplasmic/membranous HBcAg expression [34]. These results recommend that membranous expression of HBsAg is directly related to active viral replication but is possibly not accountable for liver cell damage, and that hepatocytes with cytoplasmic/membranous HBcAg expression might be possible targets for immune hepatocytolysis [34].

Less is known about the mechanisms that control the loss of immune tolerance in chronic HBV infection. The finding that immune clearance phase is together with an alteration in the intrahepatic distribution of HBcAg from nuclear to cytoplasmic localization advocates that it may be activated by variation in the presentation of viral antigens. But, more current study recommends that the transfer of hepatocyte HBcAg from nucleus to cytoplasm during the immune clearance phase may be secondary to liver cell injure and revival [38].

Hepatitis activity and acute Hepatitis flare during Immune Clearance Phase (HBeAg positive chronic Hepatitis): The majority of the patients in the immune clearance phase are asymptomatic and have mild to reasonable increase in ALT levels and hepatitis activity, so called HBeAg positive chronic hepatitis B (CHB). But, the clinical track may be interrupted by impulsive acute hepatitis flare, defined as a sudden elevation of ALT >5 times the upper edge of normal (ULN). These acute hepatitis flares are believed to be the results of HLA-class I antigen-limited, CTL mediated immune response against HBV antigen(s) and its downstream apoptotic mechanisms [39]. The causes for spontaneous acute hepatitis flares are not obvious but are possibly elucidated by slight changes in immunological controls of viral replication. Numerous studies have found that acute hepatitis flares are often preceded by an abrupt boost in serum levels of HBV DNA [40, 41]. HBeAg and HBeAg-specific immune compounds [41] and improved T-cell response to HBcAg and HBeAg [42]. These findings advocate that increases in viral replication, accumulation of nucleocapsid proteins in serum and hepatocytes, and the following immune response play a vital role in initiating acute hepatitis flares in chronic HBV infection [41]. Histological confirmation of lobular hepatitis superimposed upon the alterations of chronic viral hepatitis is often examined [43]. IgM anti-HBc is positive in 14.4 % of patients through acute flares, but normally in lower titers than in acute HBV infection [44]. As HBeAgn sero exchange is often preceded or accompanied by a transient ALT flare, it is assumed that hepatitis flares are the results of the host effort to clear the virus by the immune response. However, not all acute hepatitis flares lead to HBeAgsero- conversion and HBV DNA clearance from serum, a phenomenon termed as “ineffective or abortive immune clearance” [39]. In this perspective, the patients may experience frequent episodes of acute hepatitis flares, which can lead to increased threat of HBV-related cirrhosis.

An early hospital-based study from Taiwan showed the annual rate of acute hepatitis flare in patients with HBeAg positive CHB was as high as 28.6 percent [45]. While, in another study that followed up asymptomatic patients beginning at the immune tolerance phase through HBeAg seroconversion, the overall occurrence of acute hepatitis flare was 28.8 % during immune clearance phase (mean 3.7 years), with 7.8 percent annual rate only [46]. Most acute hepatitis flares are asymptomatic, however about 20 percent of patients currently having symptoms of obvious acute hepatitis [44], and approximately 2–3 % may be complicated with hepatic decompensation [47]. Recently a report from Taiwan establish that a serum HBV DNA level ≥1.55 × 109 copies/

mL at the onset of acute flare can predict hepatic decompensation [48]. In high HBV prevalence areas, acute hepatitis flares of chronic HBV infection are the most significant etiology of acute hepatitis and fulminant hepatitis in adults [49,50].

HBeAg to Anti-HBeSeroconversion: The immune clearance phase has a variable period and often preceding for several years until HBeAg seroconversion occurs. HBeAg seroconversion is often prolongs with the increase in ALT, followed by an obvious decline in serum HBV DNA levels that can only be noticed by sensitive polymerase chain reaction (PCR) assay, reduction of serum HBsAg level, ALT normalization and resolution of liver necro inflammation [39, 40, 41, 42, 43]. However, high-level HBV DNA and abnormal ALT levels endures at the time of HBeAgseroconversion in about 5 % of patients [51]. These patients progress directly from HBeAg positive chronic hepatitis to HBeAg negative chronic hepatitis.

The average annual prevalence of HBeAg seroconversion is 10 % (range, 2–15 %), depending on features such as ethnicity, mode of transmission, age, ALT levels, histological activities and HBV genotype. In children HBeAg seroconversion is much more delayed in mothers caring HBeAg positive than in children with HBeAg negative carrier mothers or children with non-carrier mothers [52]. Various methods of HBV transmission accounts for the much lower HBeAg positivity rates in black Africans of childbearing age than in women in the Far East [3, 36]. An elevated HBeAg seroconversion rate has been described in non-Asian children with horizontal transmission than Asian children with vertical transmission [53]. The likelihood of HBeAg seroclearance correlates positively with ALT levels: HBeAg seroclearance rates at 18-months of follow-up are 0, 3–8, 17, and 59–70 %, respectively, if baseline ALT levels raised over <1, 1–2.5, 2.5–5, and >5 times ULN [39]. In patients with acute hepatitis flare, 72 % undergo HBeAgsero- clearance within 3 months if serum α-fetoprotein (AFP) levels >100 ng/mL, compared to only 18 % of those with AFP <100 ng/ml [54]. Serum HBV DNA levels ≤7 log10 copies/mL during acute hepatitis flare also can predict HBeAg seroconversion within 6 months [55]. The likelihood of BeAg seroconversion also associates with histological activities: the 5-year increasing probabilities of HBeAg seroconversion is >65 % in patients with high necro inflammatory (interface or lobular) activities, compared to <25 % in those with low necro inflammatory activities. HBeAg seroclearance may incidence within 3 months in two-thirds of the patients with bridging hepatic necrosis [54]. Patients infected with genotype B HBV seroconvert earlier and more often than those with genotype C HBV in Eastern countries [50,56,57]). While in Western countries, HBeAg seroconversion is parallel in genotypes A, B, D, and F HBV infection but much slower in genotype C HBV infection [58, 59] HBeAg seroconversion is more repeatedly preceded by ALT flares >5 times ULN in genotype C HBV infection than in genotype B HBV infection, signifying that a stronger immune-mediated hepatocytolysis may be required to achieve HBeAg seroconversion in genotype C HBV infection [50].

HBeAg persistence and its outcome: The immune clearance phase in several patients, may last for numerous years without HBeAg seroconversion. An extended HBeAg positive phase is linked with increased risk of disease progression. A latest cohort study established that the risk of progression to cirrhosis enlarged with growing age of HBeAg seroconversion, with a hazard ratio of 3.8 per decade increase in age of HBeAg seroconversion [46]. In particular, patients with HBeAg seroconversion after 40 years of ages were related with an extremely high risk of progression to cirrhosis [60, 61]. A number of other studies also explained that persistence of serum HBeAg was coupled with an improved risk for progression to cirrhosis, HCC increase and liver related mortality [62, 63, 64]. For example, in one study that followed up 233 untreated patients with HBeAg positive CHB for a middle of 6.8 years, the annual rate of cirrhosis and HCC development was drastically higher in 147 patients with constant HBeAg (3.7 and 1.6 %, respectively) than in 86 patients who underwent HBeAg seroconversion (1.8 and 0.4 %, respectively) [63].

Low Replicative Inactive Phase: Serum HBeAg is seroconverted to anti-HBe after successful immune clearance. The patients are still positive for HBsAg, however there is generally a >1 log10 IU/mL decrease in HBsAg levels, Parallel to preceding immune clearance phase, and HBsAg levels seldom surpass 1000 IU/mL during this phase [31, 32, 33]. The prominent result of HBeAg seroconversion generally signals a transition from CHB to an inactive

carrier state. HBV DNA is usually untraceable by hybridization practices but frequently visible via PCR assays. The patients are asymptomatic and have normal ALT. Liver biopsy indicates no or gentle necro inflammatory activity with uneven degrees of fibrosis, together with inactive cirrhosis. HBsAg is allocated completely in hepatocyte cytoplasm and intrahepatic HBcAg is missing [34]

Most of the inactive transporters had levels of HBV DNA less than 2000 IU/mL, a level that has been used to differentiate inactive carrier state from HBeAg negative chronic hepatitis [65]. However, a current study in 250 inactive carriers with steadily normal ALT for more than 10 years indicated that only 64 % had levels of HBV DNA <104 copies/mL, and 26 and 10 % had levels of HBV DNA in the range of 104–105 and 105–106 copies/mL, respectively [66]. Therefore, it should be more suitable to choose HBV DNA levels of 20,000 IU/mL, instead of 2000 IU/ mL, as a cut-off value to distinguish active from inactive HBV infection [67].

The majority of inactive carriers stay in this phase with constant remission and a life-long inactive state, especially if this phase is get to early in the disease course. The prediction of inactive carriers from intermediate- or low- incidence areas is even better, perhaps due to the shorter interval of the infection [68, 69].

Reactivation of hepatitis B

Following HBeAg seroconversion, a group of patients eventually undergo impulsive reactivation of HBV replication, with re-emergence of high levels of HBV DNA (>2000 or 20,000 IU/mL) and an increase in ALT levels. Just a minute proportion of carriers with HBV reactivation is linked with reappearance of serum HBeAg (HBeAg reversion) and the rests are persistently HBeAg negative [46, 51], suggesting that reactivation of hepatitis B generally results from HBV variants with procure or BCP mutations. Additionally, HBV replication can reactivate as a result of immunosuppression or cancer chemotherapy [70].

HBeAg reversion: 109 (20 %) of 541 seroconverters developed HBeAg reversion in a study from Alaska, which was often accompanied by hepatitis flare, and HBeAg tended to vary between seroconversion and reversion [71]. HBeAg reversion, however, is much rare in other studies. In another study from Italy, only one (1.6 %) of 61 seroconverters had HBeAg reversion during a mean follow-up of 22.8 years [64] regardless of the low frequency, HBeAg reversion is drastically linked with greater risk of progression to cirrhosis as well as development of HCC [51] [52] [53] [72] [54] [55] [37] [57] [50] [58] [59] [60] [61] [62] [63] [64] [65] [66] [67] [68] [73] [70].

Reactivation leads to transplantation

Reactivation of hepatitis B refers to the sudden increase of hepatitis B virus (HBV) replication in a patient with inactive or resolved hepatitis B. Reactivation arises spontaneously, but more typically is emerged by immunosuppressive therapy of cancer, autoimmune disease, or organ transplantation. Reactivation can be transient and clinically silent [74] but often causes a flare of disease that can be severe resulting in acute hepatic failure. Most instances of reactivation resolve spontaneously, but if immune suppression [75] is continued, re-establishment of chronic hepatitis occurs which can lead to progressiveliver injury and cirrhosis. The best-described instances of reactivation occur in hepatitis B surface antigen (HBsAg) carriers with inactive or minimally active disease who aregiven cancer chemotherapy for lymphoma or leukemia. Typically, serum HBV DNA rises during chemotherapy, followed by a disease flare and HBV DNA clearance with immune reconstitution after chemotherapy is stopped. Special forms of reactivation occur after solid organ and bone marrow transplantation in which chronic infection often results. Several randomized, placebo-controlled trials have shown that reactivation can be prevented by antiviral prophylaxis [76].

Complications

Cirrhosis is the result of Chronic HBV infection and its complications, including ascites, portal hypertension, hemorrhage, and hepatocellular carcinoma. Hepatocellular carcinoma observation in patients with chronic HBV infection is frequently performed every six to 12 months using α-fetoprotein levels and abdominal ultrasonography [65, 77] however, a Cochrane review establish inadequate proof to show that hepatocellular carcinoma surveillance improves survival [78]. A randomized trial of 18,816 persons with chronic HBV infection found a 37 percent increase in survival at one year in those screened against

those not screened [79]. A latest meta- analysis of six studies having 2,984 patients found a joint sensitivity of 94 % and a mutual specificity of 94 % for screening ultrasonography, with screening every six months better to screening every 12 months (P = .001) [80]. Hepatocellular carcinoma is comparatively rare in the United States (2.8 cases per 100,000 white men and 6.1 cases per 100,000 black men), but the frequency has enhanced 71.4 percent over past 3 decades [81].

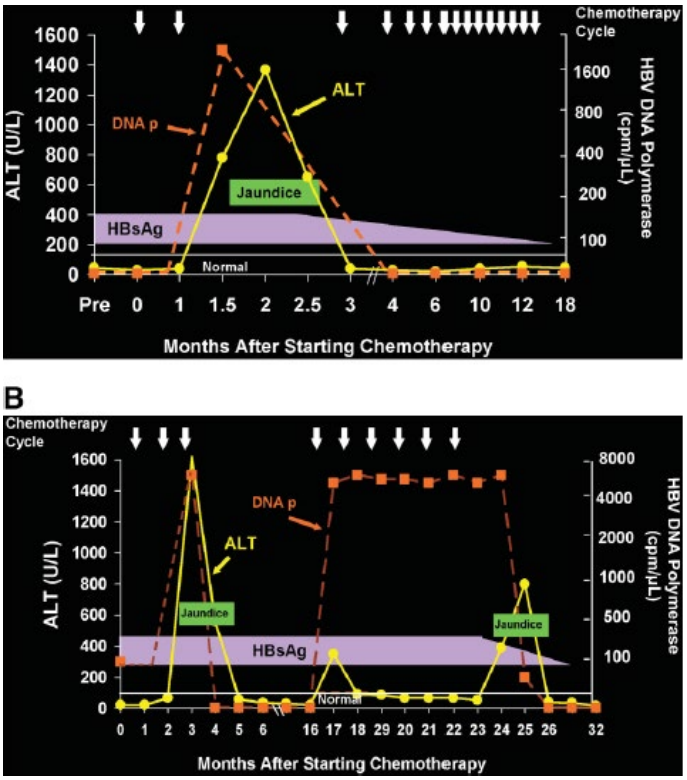

Figure 3: *Chemotherapy cycle of HBV DNA Polymerase (A) up to 18 months; (B) up to 32.*

HBV and liver transplantation

Annually worldwide, hepatitis B virus (HBV) infection doubles the number of deaths compared to hepatitis C virus (HCV) infection. According to World Health Organisation (WHO) statistics for the year 2000 more than 600 000 deaths could be attributed to HBV infection, in which nearly 400 000 deaths from primary hepatocellular cancer (HCC). However, the countries and regions of the world that have little or no access to liver transplantation (LT) bears maximum burden due to HBV infection. Thus, the incidence of HBV infection remains quite low in developed countries, and HBV is not a leading sign for LT. For example, in UK, HBV is the sign for LT in approximately 5% of cases. That number has beenquite constant during the last 10 years but might be increased as a result of migration to the UK of people from countries of high HBV occurrence. Infact, most of the transplanted HBV patients were/ are first generation migrants from high to low HBV prevalence countries. Liver transplantation for HBV should be discussed in a historical point of view. The outcome of LT for HBV has enhanced considerably for the last 20 years [82].

That enhancement reveals the improved outcome experienced by LT recipients in general, but also the important and stepwise modifications made in antiviral prophylaxis and treatment of HBV infection. Particularly, the current introduction of nucleoside analogues as component(s) of prophylaxis, and the utilization of these drugs alone or in combination for treatment of established graft infection, have transformed the outcome of LT for HBV. As a result, few if any grafts should succumb to HBV-imposed damage. HBV infection, not long ago supposed as a marginal indication for LT, is now considered an exceptional indication for LT. Superior graft and patient survival is expected.

Chronic HBV infection management (including cirrhosis) and patients selection for LT

Hepatitis B virus infection is often diagnosed during the phase of chronic hepatitis prior to the development of cirrhosis. In significant viral replication perspective, revealed by the serum HBV titre, antiviral therapy should be given. Productive and extended inhibition of viral replication can stop or hinder progression to cirrhosis, consequently preventing the progress towards liver collapse and minimizing the chances of HCC [83]. Current and ongoing advances with nucleoside analogues and new interferons, given as combination antiviral therapy, give confidence that difficulties of chronic HBV infection may be preventable. Chronic hepatitis is repeatedly asymptomatic unfortunately, and many infected patients present after development of cirrhosis. Some are diagnosed at the time of presentation with hepatic decompensation or with symptoms of advanced HCC. Positive effect of viral suppression by lamivudine or adefovir for patients with advanced cirrhosis, illustrated in numerous published series. Reliable observations included the normalization of laboratory parameters and co-incident betterment of symptoms of liver failure [84].

The potential for decree of liver failure during HBV inhibition with lamivudine created two challenges for the treating physician. The need to distinguish, at an early stage of management, was the first challenge,

those patients with liver decompensation that would or would not resolve during antiviral treatment. Progress is monitored during the first 3–6 months of treatment and continued for as long as repression of viral replication is maintained. Patients with more severe decompensation at presentation are prone to die during short-term surveillance, and less likely to rally as a benefit of viral suppression [85]. Great number of recipient waiting lists and long waiting times allowed patients to segregate into those that would improve considerably as a benefit of antiviral therapy, and those that would die regardless of viral suppression during short-term follow up. Less waiting times did not allow that segregation. Therefore, patients with more severe disease at presentation were recovered by early transplantation. Though, various patients were transplanted even though they had the capability for the recovery without transplantation. That issue persists in spite of the advancement in antiviral protocols and repertoire.

A second problem was faced by the selection of lamivudine-resistant HBV for long time treatment with lamivudine drug. It had accepted that the occurrence of drug- resistance before LT become the cause of two problems. The HBV replication decompensate to pretreatment level in some patients. Also, the benefits of lamivudine [either in combination with HVB immunoglobulin (HBIg) or alone] as prophylaxis were proved against graft infection when serum titers rose before LT to pretreatment levels. Thus, lamivudine treatment proves a good treatment for LT when the liver function improved while before the occurrence of drug resistance. The problem for the clinician was, of course, that it was impossible to gauge the width of that window. For a specific patient, the duration of treatment could be predicted accurately but before resistant emergence. That doubt needed understanding with the uncertainties of waiting list management. This dilemma worried physicians after the availability of lamivudine and before ready access to adefovir, during the period 1995–2000 (approximately). Lamivudine-resistant HBV patients could me cure by the treatment of adefovir which suppress the replication of HBV for long time treatment. It has been discussed that the addition of adefovir for lamivudine- resistant HBV provides good prophylaxis but before transplantation against post-LT graft infection.

In conclusion, via antiviral therapy the chronic progenies of HBV had been cured. Mostly patient attained the viral replication suppression with drug available in market. For the patient treated before the development of cirrhosis, cirrhosis and its complications should be prevented. For the patients with well compensated cirrhosis, sustained suppression should prevent hepatic decompensation and reduce the risk for development of HCC. For the patient with hepatic decompensation in the context of viral replication, antivirals may restore a well-compensated cirrhosis and prevent need for transplantation. The net effect may be to decrease the number of patients with decompensated HBV undergoing LT. Of course, despite the beneficial impact on risk for HCC, surveillance for HCC will be essential. Many may develop HCC during prolonged follow-up. It seems probable that the net effect will be that future cohorts transplanted for chronic HBV will be somewhat older and more likely to be transplanted for HCC than for decompensated cirrhosis.

Management of fulminant HBV and selection of patients for LT

Fulminant HBV is mainly adults affecting uncommon disease. Commonly causes through sexual transmission, however a considerable proportion is infected by injecting drug use. Fulminant HBV patients selected for LT first needs an evaluation of prediction for survival with conventional management. LT is suitable treatment if the prognosis for survival is significantly enhanced by LT. Additionally, the likelihood of conformity with post-LT care requires to be considered. For example, fulminant HBV occurring in the perspective of chaotic drug use might be more suitably managed without LT. Under these conditions, and in spite of the necessity, it seems appropriate to set equal standards to those that are posed for patients with substance abuse that suffer with HCV or alcohol-related liver failure. The majority of the clinicians agree that active intravenous drug use is a complete contraindication to LT. We experienced that, post-LT observance with follow-up has been very poor by those patients transplanted for acute HBV in the context of injecting drug use.

Patients with fulminant HBV, the possible role for antiviral treatment remains doubtful. Currently published series verified that serum HBV titres are fairly high (frequently in excess of 1 million genomic copies/mL serum) at presentation time with acute and fulminant infection [86, 87]. Even though, prospective

controlled clinical trials not shown, available data involve that rapid antiviral treatment with lamivudine may be useful. Such as, [87] described their experience by organizing of 15 consecutive cases of severe acute hepatitis B infection, including five patients with hepatic encephalopathy. The mean serum titre for the cohort at presentation was higher than 107 copies/mL, and all were cured with lamivudine. Thirteen stay alive without the need for transplantation. Therefore, there may be a validation for antiviral therapy at the time of presentation, prior to the accessibility of serum HBV DNA measurements. While patients with fulminant HBV that progressed to LT, the involvement of a short period of pre-LT lamivudine to success of post-LT prophylaxis is mysterious.

Risk assessment

HBV replication status at transplant: For HBV recurrence existence of a replicating virus pre-transplant is greatly prognostic. A serum HBV DNA ≥ 5 or 6 log10 copies/mL at transplant has always been observed to be coupled with post-transplant HBV recurrence [88, 89, 90, 91]. Mounting data sustain the safety and efficacy of newer NA (Nucleus /tide analogues) in patients with decompensated liver disease because of HBV, thus extra patients are estimated to benefit from achieving an untraceable HBV DNA in serum at transplant, which directs to a lesser risk of HBV recurrence post-LT [92]. A randomized prospective study on 112 patients with decompensated HBV cirrhosis demonstrated that most of the patients who received TFV, emtricitabine /TFV, or ETV were capable to attain a low level of HBV DNA < 400 copies/mL (69 IU/mL) at week 48 (70%, 87%, and 72%, respectively) [93]. In contrast Fulminant hepatitis B is connected with a lesser risk of HBV recurrence [94].

LAM resistance: Appearance of drug resistance as on post-LT prophylaxis or existence of LAM-resistant HBV pre transplant has been constantly prognostic of HBV recurrence. Identifying drug-resistance particularly pre-transplant would decide the high-risk patients who possibly benefited from a conventional approach, including a combination of HBIG plus NAs. Combination of LAM plus either ADV or emtricitabine have revealed effectiveness with a low recurrence rate of HBV post LT. In non-transplant patient's newer antiviral drugs used either alone or in combination are obviously better to LAM and ADV, and as described earlier, single or combined regimens of newer NAs are also efficient for HBV prophylaxis in post-LT setting when used with or without HBIG. No resistant HBV was noticed at 3-year post-transplant in the study by [88] in patients on ETV monotherapy.

Authors Contribution

Idea was generated by ZS, data was acquired by SAL, JHT and JQ and manuscript was written by SAL, ZL and WJ.

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