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REVIEW ARTICLE

Hepatitis B virus infection in Iran

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1. Epidemiology of hepatitis B

1.1. Global epidemiology and burden of HBV

HBV infection is a worldwide major health problem. About 2 billion people have been infected with this virus and 350 million of these are chronically infected (or carriers) with the virus (1). The global prevalence of chronic HBV infection varies widely and world can be divided into three categories of HBV prevalence; high (prevalence of about 8%), intermediate (prevalence of 2-7%) and low (prevalence of fewer than 2%) (2). Despite the availability of effective HBV vaccines, new infection is common. The incidence of new cases of HBV is about 200/000-300/000 in USA and 1 million in Europe each year (3,4). Worldwide, 350 million people with chronic HBV infection have a 15% to 25% risk of dying from HBV-related liver disease, including cirrhosis and hepatocellular carcinoma (HCC) (5). HBV is estimated to be responsible for 500,000–700,000 deaths each year (6,7).

1.2. Epidemiology of disease in Iran

Iran is located in the intermediate area of HBV prevalence. In the previous studies, it was estimated that over 35% of Iranians have been exposed to the HBV and about 3% are chronic carriers, ranging from 1.7% in Fars Province to over 5% in Sistan and Balouchestan (8). In some populations the rate of infection may be even higher (e.g. 15.5% rate of positive HBsAg in gypsy population in Shahr-e-Kord (9). In a sample of 250/000 apparently healthy blood donors in Tehran, HBc antibody was detected in 37% of this population, further 3.6% of male and 1.6% of female donors were HBsAg carriers. Thus, it appears that 8% of Iranians infected by HBV become chronic carriers (10).

It is evident that 70-84% of cirrhotic patients and 72% of patients with hepatocellular carcinoma (HCC) in Iran have evidence of exposure to HBV with a carrier rate of 46-56%, respectively (11,12). These data suggest that HBV is the most common cause of cirrhosis and HCC in Iran. Following the HBV neonatal vaccination in Iran and in some other Middle East countries including Bahrain, and Kuwait, which all reach over 80% of the population as part of their Expanded Programme on Immunization (EPI), it is expected that by now the prevalence of HBsAg carrier rates in general population in these countries decreased to fewer than 2% (13).

2. Transmission modes

Persons with chronic HBV infection are the major reservoir for transmission. HBV is present in the blood, saliva, semen, vaginal secretions, menstrual blood, sweat, breast milk, tears and urine of infected individuals (14). HBV can be transmitted by perinatal, percutaneous and sexual

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exposure, as well as by close person-to-person contact, presumably by open cuts and sores, especially among children in hyperendemic areas and also in occupational/health-care-related (5,15,16).

Transmission from a chronically infected woman to her infant during delivery is efficient and is one of the most common routes of HBV infection worldwide. Perinatal transmission of HBV most often occurs during the birth process; in-utero transmission can occur but is rare and accounts for less than 2 percent of perinatal transmissions (17,18). The risk of perinatal infection is 5–20 percent in infants born to HBsAg-positive mothers and 70–90 percent if the mother is HBeAg-positive (19). Prenatal transmission might be one of the common routes of transmission in Iran since the result of one study revealed that over 50% of mothers of HBsAg positive individuals were also carriers (20). It may be concluded that over 50% of Iranian carriers have contracted the infection prenatally making this route the most likely route of transmission of HBV in Iran.

HBV is efficiently transmitted by sexual contact (21). Sexual transmission of hepatitis B occurs worldwide. The risk increases with the number of partners, years of sexual activity, history of other sexually transmitted infections, and with anal intercourse. Sexual contacts of chronically infected persons have been shown to have a higher seroprevalence of HBV infection than control populations, including household (nonsexual) contacts of infected persons (22) . In Iran over 75% of the wives of male Iranian carriers have natural immunity against HBV (20). Men who have sex with men have high rates of disease and they have persistently higher HBV seroprevalence rates than the general population (23,24).

Health care environment is another source of viral transmission which is mostly related to the level of blood and needle exposure. Patient-to-provider transmission was common before widespread hepatitis B vaccination of health care workers. The risk of disease transmission after needle stick is 30% with HBeAg positive blood and less than 6% if blood is HBeAg negative (25).

Also disease might transfer from a HBV positive health care worker to the other patients under his or her care (patient-to patient transmission) in the medical environments. Patient-to-patient HBV transmission is a major source of new HBV infections in the developing world. HBV can survive outside the body for prolong period, and carriers who are HBeAg positive can shed large amount of virus (10^{7-9}) on environment through open wound (26,27). Thus, since HBV can remain stable and infectious on environmental surfaces, transmission may occur indirectly via contaminated surfaces and other objects (28). Patient-to-patient HBV transmission can result from percutaneous exposure to contaminated equipment used for injections or other procedures, or from blood or mucosal exposure to contaminated medication. This might happen more in developing countries mostly because of lack of awareness of infection control practices and lack of resources for sterilization and the purchase of new disposable equipment. Contaminated injections caused an estimated 21 million HBV infections worldwide in 2000, accounting for 32 percent of all new infections (29). In study performed on the health workers of the National Iranian Oil Company (NIOC), 23% had evidence of exposure to HBV and 1.8% had a positive HBsAg. In this study, the laboratory personnel were found to be at higher risk than other health workers (30)

Injection drug users are at high risk for HBV infection because of behaviours such as sharing of needles, syringes, and other high risk behaviours. It has been estimated that globally 8–16 million new HBV infections occur annually due to unsafe injections (31). The result of an unpublished data showed that over 25% of intravenous drug users in prison (8.4% of all prisoners) in southern Iran were HBV carriers.

3. Virology and molecular epidemiology

Human HBV is the prototype for a family of viruses referred to Hepadnaviridae. These viruses have a strong preference for infecting hepatocytes, which are the only confirmed site of replication for all members of this family (32). Small amounts of hepadenaviral DNA can be found in other organs such as the kidney, pancreas, and mononuclear cells, but infection at these sites is not related to extrahepatic disease (33-36). Phylogenetic analysis has led to the classification of HBV into eight genotypes, A-H, defined by inter-group divergence of >8% in the complete genome (37-40).

A distinct pattern of geographical distribution of HBV genotypes has always been evident and is reinforced by recent findings(41,42) (table 1). In fact genotyping can help to trace the migration of ancestors as well as the routes of transmission in accidental exposure to HBV.

Since Iran is located in Mediterranean area it is expected that our predominant genotype is D. Thus, the result of a study among 5 HBsAg positive patients from Iran revealed that they were infected with HBV genotype D (43).

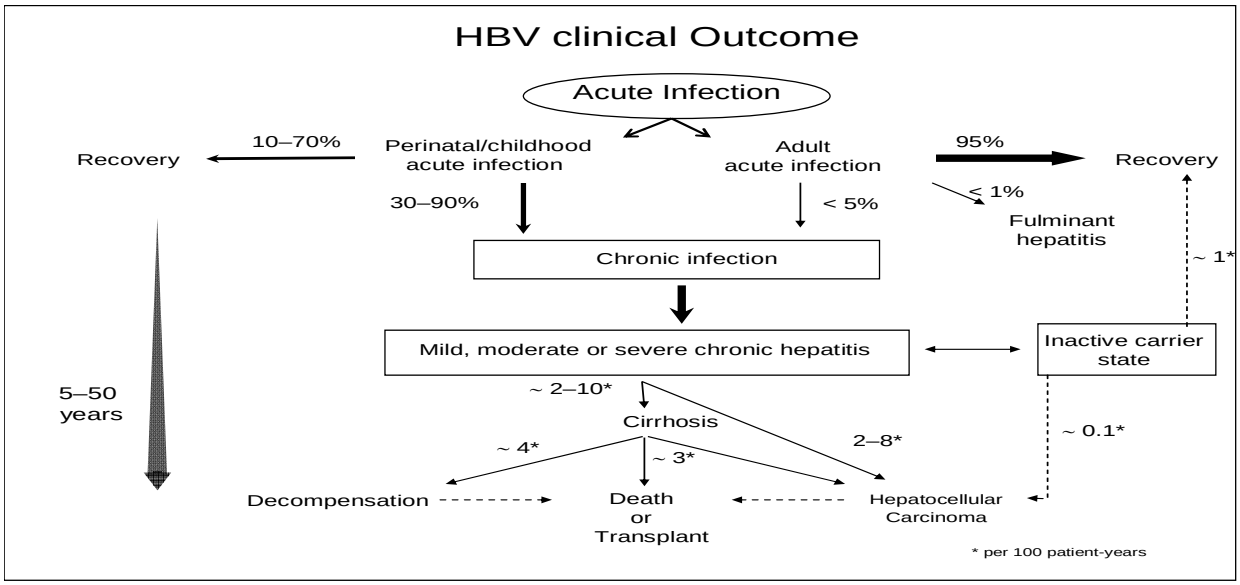
Also, recently (unpublished data) the full genome of 24 patients have been studied and this result confirmed that all strains were classified into genotype D and sub-genotype D1, with bootstrap values of 99%.

Table 1. *Geographical distribution of HBV genotypes*

Genotype	Geographic distribution
A	Northwest Europe, sub-Saharan Africa, North, Central and South America
B	Southeast Asia, China, Japan, Oceania
C	Southeast Asia, China, Japan, Oceania
D	Mediterranean area, Central Asia and South America
E	West Africa
F	Central and South America

4. Natural history of HBV

Figure 1 shows clinical outcome of HBV infection. HBV Infection can cause a wide range of disease from acute and fulminant hepatitis to chronic disease resulting in cirrhosis and HCC. Acute hepatitis usually happened in adult individual who have a mature immune system and show a rapid reaction to the virus. A chronic hepatitis B situation is defined by the presence of



Adapted from EASL Consensus Statement. J Hepatol 2003; 39 (S1):S3–25

Figure 1. *Clinical outcome of HBV infection*

HBsAg and a persistent increase of serum aminotransferase (ALT) level for more than 6 months after infection. The risk of developing chronic HBV infection after acute exposure ranges from 90% in newborns of HBeAg-positive mothers, through 25%-30% for infants and children under 5 years of age, to less than 5% in adults (44-48).

4.1. Acute infection

According to WHO estimation, in 2000, there were over 5.2 million cases of acute hepatitis B infection worldwide (49). Acute hepatitis B is probably the most common cause of hepatitis among Iranian adults. Acute HBV is generally subclinical in neonates and children; by contrast 30–50% of adults might develop icteric hepatitis (47). About 0.1 to 0.5% of acute cases will progress to fulminant hepatitis. Hepatitis B is the most common cause of fulminant hepatitis in Iran (10). Such patients present with encephalopathy, spontaneous bleeding due to coagulopathy, and a progressive decrease in liver span. It is generally believed that fulminant hepatitis is due to a severe immune response of the host resulting in inhibition of viral replication and massive lysis of infected hepatocytes, this explaining the absence of serological markers of HBV infection in many patients(50). The mortality of fulminant hepatitis B is over 80% and its standard treatment is urgent liver transplantation. However, recent data suggest that a 6 month course of lamivuine may be effective in some patients with sub-fulminant or fulminant hepatitis B (51). Following fulminant HBV infection the recurrence of HBV in a liver transplant is uncommon.

4.2. Chronic HBV infection

Based on virus-host interactions, the natural history of chronic HBV infection acquired prenatally can be divided into three phases (summarised in figure 2) (52-55). In the first highly replicative or *immune tolerance* phase, patients are HBeAg positive and have high serum HBV-DNA concentrations, but there are no symptoms; serum ALT levels are not raised, and the liver shows minimal inflammatory activity. During the second low replicative or *immune clearance* phase, a proportion of previously symptom-free HBV carriers develop exacerbated chronic hepatitis B and may manifest clinical features of acute hepatitis. Such an acute exacerbation occurs when the previously existing immune tolerance no longer persists. Subsequently, the hepatocytes that harvest actively replicating HBV are eliminated by a T-cell (CD8) mediated immune reaction in blood. The annual rate of HBeAg sero-clearance is estimated to be 5-15% (56,57). The majority of patients in this immune-reactive phase develop liver damage which may even reach advance stage of fibrosis or cirrhosis, if HBeAg persist for a longer time. This leads to the third *non-replicative* or residual integrated phase, when serum HBsAg persists but HBeAg and HBV DNA are no longer detectable. Patients are usually symptom free and liver disease becomes inactive. Seroconversion from HBeAg to anti-HBe indicates a favourable outcome, because it is usually associated with the cessation of HBV replication and non-progressive liver disease. In most patients who have undergone HBeAg seroconversion, the level of HBV DNA decreases below the detection levels of non-PCR based assays (typically $<10^5$ copies/ml), aminotransferase (ALT) levels normalize, and necro-inflammation decreases. These patients are usually referred as the *inactive* HBsAg or HBV *carrier* state. Some patients may also lose HBsAg and seroconvert to HBsAb (58). However, with very sensitive techniques as the polymerase chain reaction (PCR) and the nested PCR assay, residual amounts of HBV DNA can be detected in the serum of most HBeAg-negative subjects (59). Follow-up studies and epidemiologic observations in HBeAg-negative patients have clearly shown that these patients may go to *reactivation* phase and develop chronic hepatitis many years after HBeAg seroconversion and in some individual, disease progresses to cirrhosis and HCC (60-63).

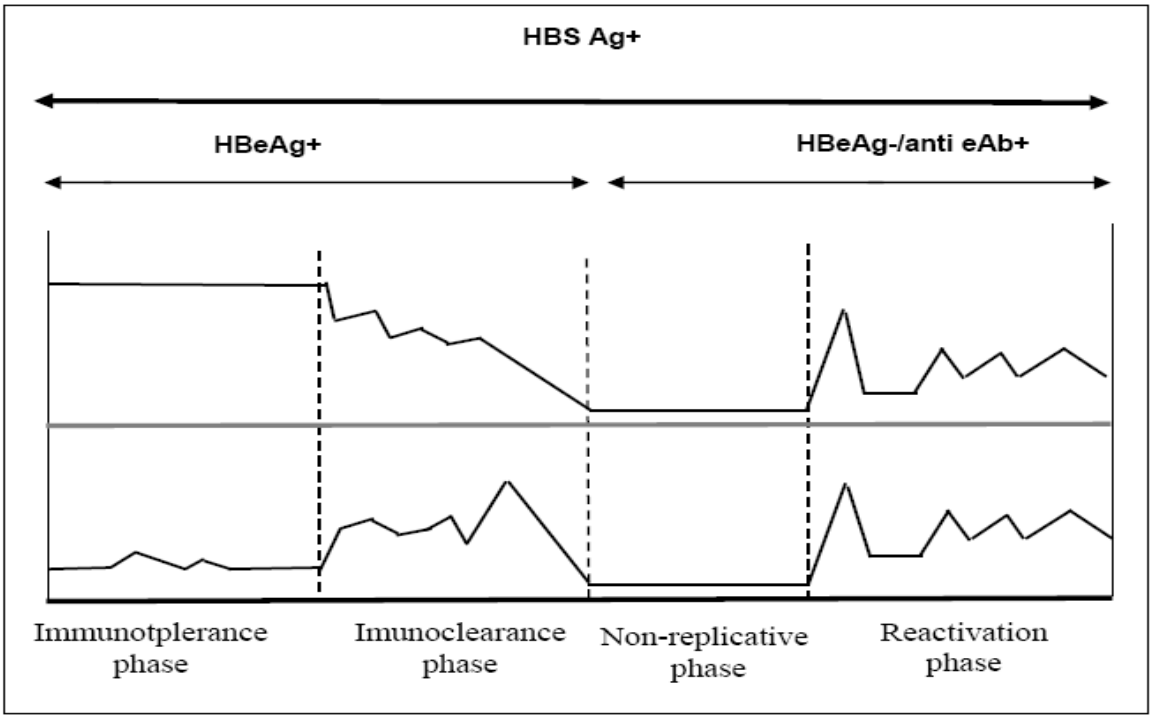


Figure 2. *Schematic representation of the natural history of chronic HBV*

The observation that HBeAg positive patients are younger than HBeAg negative HBV carriers (64) supports the concept that HBeAg negativity represents the later stage of the natural course of chronic HBV infection. Sequencing of the genome of the virus in HBeAg negative patients has revealed that in most cases the virus belongs to variants that are unable to produce HBeAg or the mixtures of these mutants with wild-type HBeAg-positive HBV. Two important groups of mutations have been described: those occurring in the pre-core region and those occurring in the basic core promoter (BCP). The dominant pre-core variant is a point mutation from a G to A at nucleotide (nt) 1896 (G1896A) which match with T at nt 1858, that creates a premature stop codon at codon 28 which terminates the translation of the pre-core/core protein and interrupts HBeAg synthesis. The most common BCP variants are at nt 1762 (A1762T) and at nt 1764 (G1764A), which reduce the pre-core RNA level and consequently reduce HBeAg production on transcription level (65,66).

4.2.1. Selection of HBeAg negative HBV mutants

In early phase of disease, the presence of circulating HBeAg is likely one of the most significant factors determining the immune tolerance of the host to the replicating virus. It is well established that this protein possesses unique tolerogenic properties (67). Presumably it crosses the placenta and induces immune tolerance in the fetus, which leads to chronic HBV infection (68,69). HBeAg has been also shown to down-regulate the host antiviral immune defences (70). It is not clear why, but, at a certain point during the course of chronic infection, immune system loses its tolerance to the replicating wild-type virus and start clearance of HBeAg (immune clearance phase). Once immune pressure to the wild-type virus starts to increase, selection of HBeAg-negative mutants and their predominance over the wild-type HBV is accelerated (71,72). But it remains to be determined why HBV mutants that are not producing HBeAg would prefer to become

selected over the wild-type virus during or after HBeAg loss and seroconversion. HBeAg-negative mutants most likely exhibit certain biological properties that make them less vulnerable to host immune reactions compared with wild-type HBV.

Ongoing HBV replication (mutant or not) in HBeAg-negative individuals triggers strong immune responses against the virus which consequently causes inflammation in the liver which is reflected by increases in serum ALT level (73). Long-term follow-up studies and epidemiologic observations in HBeAg-negative patients have clearly shown that the development of CHB may occur years or decades after HBeAg seroconversion (71,74).

The result of many studies showed that core promoter and BCP are associated with severe and advanced liver disease (65,75-78). In a study among Iranian patients, mutation at BCP and older age were independent predictor of cirrhosis and HCC. In this study, it was found approximately 4 folds increase risk for advanced liver disease (cirrhosis and HCC) among patients with mutation at T1762-A1764. This mutation also happened in patients with significantly higher level of ALT and viral load (Poustchi, et al. unpublished data).

The prevalence of HBeAg-negative CHB seems to vary geographically and has been reported to be more prevalent in the Mediterranean basin, the Middle East and Asia (79). Possible contributing factors for its development include vertical transmission of HBV, long duration of infection and male sex (80,81). Recent data suggest that HBeAg negative chronic hepatitis is more common than previously suspected and that is present worldwide. In recent community-based studies from different parts of the world, the prevalence of HBeAg negativity in chronic HBV infection has been found to range between 70% and 100% (79).

Both HBeAg seroconversion and development of chronic HBV in HBeAg-negative patients is associated in a great extend with the infecting HBV genotype thus, seroconversion to HBeAg negative and progression of disease to chronic HBV have been reported more frequently and earlier in HBV genotype D compare with genotype A or C (82). Since the predominant genotype of HBV in Iran is genotype D (43), it can be concluded that most of the Iranian with chronic HBV are eAg negative. In a recent study, 83% of consecutive chronic HBV carriers in a referral center in Iran had negative HBeAg (64).

In general, the long-term prognosis of HBeAg negative CHB patients is poor. A higher rate of cirrhosis has been reported in HBeAg negative patients compare with HBeAg positive patients (83). In Italy, one third of patients have been found to develop cirrhosis over a mean period of 6 years (62). In another study in Greek (predominate by HBV genotype D), 29% mortality rate was reported in only 4 years after disease presentation and 14% incidence of HCC in the same time period, being much higher compared with a group of patients with HBeAg-positive CHB (84). Higher rate of cirrhosis in HBeAg negative patients may be related to the fact that HBeAg negativity represents a later stage in the natural history of chronic HBV infection, and some of HBeAg positive patients may develop cirrhosis after HBeAg seroconversion and after several years of chronic liver injury.

6. General recommendations for HBV carriers

All chronic HBV carriers should be counseled about routes of HBV transmission. Those who are in close contacts with HBV carriers should undergo screening with HBsAg and HBsAb; and HBV vaccination should be performed for at risk individuals. All patients should be discouraged from heavy alcohol use, and abstinence from alcohol is recommended for those with cirrhosis (85,86). All HBV carriers should screen for HCV infection. Also, screening for hepatitis D virus (HDV) infection should be performed using HDV Ab in areas with higher rates of HDV infection (e.g. southern parts of Iran).

Hepatitis B virus carriers are at increased risk for the development of hepatocellular carcinoma

(HCC) (87). HCC can be detected early with periodic alpha-fetoprotein (AFP) and ultrasound screening. HCC screening with periodic AFP and ultrasound (e.g. every 6 months) should be considered for HBV carriers at high risk for HCC (i.e., men > 45 yr, persons with cirrhosis, and those with a family history of HCC). It is important to be aware that in patients with hepatitis B, HCC can occur in the absence of cirrhosis (86,87). Periodic screening for HCC by using AFP should be considered in low-risk individuals from endemic areas (86).

7. Treatment for HBV

7.1. Patient selection for treatment

7.1.1. HBeAg positive patients

In patients with HBeAg-positive chronic hepatitis B and with evidences of active disease, treatment should be initiated if spontaneous seroconversion is not observed after 3–6 months. If serum levels of HBV DNA are $>10^5$ copies/ml, with levels of ALT being normal, the patient is most probably in the immune tolerance phase of HBV infection and can be observed.

In patients with mildly elevated serum ALT levels (e.g. less than 2 times the upper limit of normal on several occasions) liver biopsy should be performed, and the patient should be treated if liver biopsy shows significant necroinflammation and/or fibrosis. Also, HBeAg positive patients with significantly elevated ALT levels (e.g. more than 2 times the upper limit of normal on several occasions) need to be treated.

7.1.2. HBeAg negative patients

Generally inactive carriers of HBV defined as negative HBeAg, persistently normal ALT, low HBV DNA levels (e.g. less than 10,000 copies/ml) do not need treatment. Patients with HBeAg negative chronic hepatitis B who have elevated serum ALT, high HBV DNA levels, and significant liver disease on liver biopsy, should undergo treatment. Differentiation between HBeAg-negative chronic hepatitis B and the inactive HBV carriers may sometimes become difficult. Thus, in patients with borderline findings (e.g. HBeAg negative patients with normal serum ALT, but high HBV DNA levels) liver biopsy can guide to make decision to treatment (86). In our recent study, a formula comprises of HBV DNA level, alkaline phosphatase, serum albumin, and platelet counts can predict significant liver fibrosis with a good accuracy in HBeAg negative patients (64). At the moment, this formula can be substitute liver biopsy for those who have contraindication or refuse to undergo liver biopsy.

7.2. Treatment agents

Six agents are currently approved for the treatment of chronic hepatitis B: Interferon alpha (IFN), Lamivudine (LMV), Pegylated interferon alpha, Adefovir, Entecavir, and Telbivudine. Each agent has its own advantages and disadvantages for use in the treatment of chronic hepatitis B. IFN is effective in a minority of patients; pegylated interferon is somewhat more effective than standard IFN. Both of these agents have frequent side effects that limit their tolerability. The efficacy of lamivudine is limited by the emergence of drug resistant which limits its usefulness as a long-term therapy. Adefovir, entecavir, and Telbivudine are relatively new drugs, and have fewer rates of drug resistance. Since the majority of Iranians are infected with genotype D and are more likely to be HBeAg negative, in this paper we focused more on treatment for this group of patients.

7.2.1. Interferon alpha (IFN)

In HBeAg positive patients, 4 to 6 months of IFN can lead to HBeAg loss in 33% of the patients (88). In HBeAg positive patients, the predictors of better response to IFN include higher ALT levels, lower HBV DNA levels, and active necroinflammatory disease in the liver.

In HBeAg negative chronic CHB patients, therapy with IFN at a dose of 3 to 6 MU three time a week for 12 or 24 months achieves sustained off-therapy response rate in almost 20-25% of patients with 25 to 40% of responders also losing HBsAg after several years of follow up (89). In HBeAg

negative CHB, the predictors of sustained response to IFN include early biochemical response, and longer duration of treatment (e.g. at least 12 months) (90).

The result of some studies revealed that in HBeAg negative patients, response rate in genotype A was higher than genotype D (91,92). Patients treated with IFN should be monitored very closely because of the side effects and intolerability. Approximately one third of patients might require dose reduction and 5% may discontinue their medication due to adverse events (93).

7.2.2. Pegylated interferon (Peg-IFN)

In peg-IFN, elimination of IFN by kidney is reduced, thus significantly increasing its half life and resulting in more stable plasma concentrations of interferon. Finally the number of injections has been reduced from thrice to once weekly.

Some RCTs showed the efficacy of peg-IFNs in HBeAg positive and HBeAg negative chronic hepatitis B compare with lamivudine. (94-97).

In a recent study in HBeAg negative CHB patients, virological response (as defined by serum HBV DNA below 20,000 copies/mL by quantitative PCR) was observed in 44% of patients treated with peginterferon alone, 43% of those treated with peginterferon plus lamivudine, and in 29% of lamivudine monotherapy group (97). Noteworthy, at the end of the 48-week treatment period, there was a higher incidence of lamivudine resistance in the lamivudine monotherapy group as compared with the peg-IFN plus lamivudine combination group. Recent data suggest that patients infected with the HBV genotype D - the predominant genotype in Iran- are less responsive to peginterferon (98).

7.2.3. Lamivudine (LMV)

Lamivudine is a nucleoside analogue which directly inhibits HBV DNA polymerase. The tolerability and safety of lamivudine is excellent; the incidence of adverse events is very low and also it is a relatively low cost drug. Randomized controlled trials have shown the efficacy of lamivudine in the treatment of HBeAg positive and HBeAg negative chronic hepatitis B.

In a randomized trial among HBeAg negative CHB patients (99), HBV DNA (as measured by PCR based assay) became undetectable in 70% of patients after 12 months of treatment. Serum ALT normalized in 75% of patients. However, most patients relapse after discontinuation of lamivudine (99,100).

In studies with prolonged therapy, response rates peak at 12 months and decrease after that (101). In a recent study of 4-year treatment with lamivudine, only 39% of HBeAg negative patients maintained virological and biochemical response while remained on lamivudine (102).

Lamivudine resistant mutants appeared in 10–40% of patients after 1 year of therapy, and in 50–60% of those treated continuously for 3 years (101,103). In summary, initial response to lamivuine is relatively good in HBeAg negative CHB; however, response rate progressively decreases while treatment is continued for several years. Such decrement in the response rate is due to the emergence of drug resistant mutants of HBV. Also, most responded patients develop virological relapse after stopping the treatment.

7.2.4. Adefovir dipivoxil:

Adefovir dipivoxil (Hepsera) is a nucleotide analog of adenosine monophosphate which can inhibit DNA polymerase activity. In recent trials Adefovir (10 mg/ day orally) was associated with a median decrease in serum HBV DNA of 3.47 $\log_{10}$ copies/mL at week 96. HBV DNA less than 1000 copies/ml was observed in 71%, and normalization of ALT in 73% of the patients at week 96 (104). The benefit of treatment was lost in the majority of patients who stopped treatment. However, continuing adefovir for 5 years can maintain virological response (e.g. as defined by undetectable HBV DNA PCR) in 67% of the patients (105). Resistant mutations (rtN236T and rtA181V) can be seen in 5.9 percent of patients

after 144 weeks (e.g about 3 years) of treatment (104). In summary, in HBeAg negative CHB, long term (e.g. several years) treatment with adefovir is associated with better virologic response and fewer rates of drug resistant mutants as compared with lamivudine. Also, adefovir carries a small risk of nephrotoxicity.

7.2.5. Entecavir:

Entecavir (Baraclude) is an orally administered cyclopentyl guanosine analogue that inhibits viral DNA polymerase. In a recent RCT, entecavir (0.5 mg daily) was compared with lamivudine (100 mg daily) for 96 weeks in HBeAg negative CHB (106). Undetectable HBV DNA by PCR occurred significantly more often in the entecavir group. (90 versus 72 percent). Serum HBV DNA decreased by 5.04 $\log_{10}$ in the entecavir group compared with 4.53 $\log_{10}$ in the lamivudine group. Also, the proportion of patients with ALT normalization was significantly higher in the entecavir group (90 versus 72 percent). Histologic improvement was observed significantly more often in the entecavir group (70 versus 61 percent). No resistance was observed up to 96 weeks of treatment with entecavir in nucleoside-naïve patients (106,107).

7.3. Drug resistant HBV infection:

Drug resistant mutants of HBV can develop in up to 65% of patients after 5 years of treatment with lamivudine (108). Lower rates of resistance to adefovir have been demonstrated in the clinical trials (5.9% at 3 years, 18% at 4 years, and 29% at 5 years) (104,105). The development of resistance should be suspected in patients who have a virological breakthrough infection, defined as increase in serum HBV DNA greater than 1 log10 copies/ml (e.g. 10 times increment in the viral load) from nadir during continued therapy. Also, reappearance of HBV DNA in serum after its initial disappearance during continued drug therapy is a sign of virological breakthrough infection. Re-elevation of serum ALT after its initial normalization (e.g. biochemical breakthrough), may occur in some patients with virological breakthrough infection. Sometimes, hepatitis flare (e.g. several times increment in serum ALT together with jaundice) may occur in patients with breakthrough infection. Such hepatitis flare may lead to hepatic decompensation in patients with underlying cirrhosis. The exact diagnosis of genotypic drug resistant mutants (e.g. YMDD mutants, etc) can be demonstrated by PCR assay. Several studies showed that adefovir is effective in inhibiting lamivudine-resistant HBV mutants (109,110). An important issue is that whether lamivudine should be discontinued after initiation of adefovir in patients with lamivudine resistant HBV infection. In a recent study in lamivudine resistance patients, virological breakthrough (due to adefovir resistance) occurred in 15% of those receiving adefovir monotherapy vs 4% of those receiving the combination (111). Thus, adding adefovir to lamivudine is better than adefovir monotherapy in these patients. Recent data shows that tenofovir is more effective than adefovir in patients with lamivudine resistant chronic hepatitis B (112). Although, tenfovir has not yet been received FDA approval for the treatment of CHB, it is expected that it replaces adefovir in the near future.

It has been showed that entecavir (1 mg daily) is also effective in patients with lamivudine resistance HBV infection (113). However, 9% of those with lamivudine resistance HBV infection who were treated with entecavir developed resistance to entecavir after 96 weeks of treatment (114). Although, no case of entecavir resistance has been reported in nucleoside-naïve patients treated with 96 weeks of entecavir (106,107). Thus, a cross resistance exists between lamivudine and entecavir; and entecavir may not be a good treatment option in patients with lamivudine resistant CHB.

Also, drug resistant strains of adefovir remain sensitive to lamivudine, thus in instances of adefovir resistance, lamivudine should be added to the drug regimen (115).

7.4. Treatment of HBV related cirrhosis

Patients with cirrhosis who have HBV DNA levels of more than 10,000 copies/ml should undergo antiviral treatment regardless of their serum ALT levels (116). Patients with compensated cirrhosis are better to treat with oral antiviral agents instead of IFN or peginterferon. Furthermore, IFN and peginterferon are certainly contraindicated in patients with decompensated cirrhosis. It has been shown that lamivudine or adefovir can improve liver function, and decrease child-pough score in patients with decompensated cirrhosis (117-119). In a recent controlled trial in compensated cirrhotic patients, the rates of development of hepatic decompensation, and hepatocelular carcinoma were significantly lower in lamivudine than in placebo group (120). Also, outcome of those who developed genotypic resistance to lamivudine was better than placebo group but worse than those lamivudine treated patients who did not develop lamivudine resistance (120). Rarely, complete regression of HBV cirrhosis after successful antiviral treatment has been reported (121).

Generally, patients with HBV related cirrhosis should undergo long term and indefinite antiviral therapy. Either adefovir or lamivudine can be used in patients with HBV cirrhosis. However, given the need for long term treatment, and high rates of resistance to lamivudine this drug is less suitable option for antiviral treatment in such patients. Currently, there are limited data available for entecavir in patients with advanced liver disease. Patients with cirrhosis in the phase III entecavir study were analyzed retrospectively for their response to therapy, and the results showed that entecavir was well tolerated and superior to lamivudine for the end points of histologic improvement, ALT normalization, and undetectable serum HBV DNA (115,122). Obviously, all decompensated cirrhotic patients should be placed in the waiting list of liver transplantation.

8. Summary of treatment recommendations

Treatment end-point in HBeAg positive CHB is HBeAg seroconversion. However, the goal of treatment in HBeAg negative CHB is sustained normalization of ALT together with sustained suppression of HBV DNA to very low levels (e.g. ideally undetectable HBV DNA by PCR assay, or at least a decrease in serum HBV DNA to less than 10,000 copies/ml equivalent to approximately 2000 IU/ml). HBeAg negative CHB patients who are taking oral nucleos(t)ides should be tested with periodic (e.g. every 6 months) testing of quantitative HBV DNA PCR to detect breakthrough infection. Real time PCR is the preferred method of PCR assay (115). Patients who fail to achieve at least a 2 log10 copies/ml decrease in HBV DNA after 6 months of therapy are considered as primary non-responder and changing the drug regimen should be considered in these individuals. Since, relapse after treatment discontinuation is very common in HBeAg negative CHB, most of such patients require long term (e.g. several years) treatment with oral nucleos(t)ide analogs. The exact duration of treatment with oral antiviaral drugs has not yet been clearly defined in HBeAg negative CHB. According to the recent data, 5 years treatment with adefovir may be a good option in HBeAg negative CHB (123). However, such patients should be closely monitored after treatment discontinuation. Since lamivudine has a high rate of drug resistance, it is not a suitable first line drug. In most circumstances, adefovir is the preferred drug regimen in Iran. In younger patients with higher ALT, and lower HBV DNA levels IFN or PEG IFN can be used as an alternative. In conclusion, in the recent years, the treatment of chronic hepatitis B has undergone tremendous change and continues to evolve with the advent of potent antiviral agents. However, many unresolved issues should be evaluated in further trials.

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