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EDITORIAL

Towards the worldwide eradication of hepatitis B virus infection: A combination of prophylactic and therapeutic factors

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Abstract

Hepatitis B virus (HBV) is still a global health problem, mostly because of the intermediate/high rates of HBV chronic carriers living in most Asian, African and eastern European countries. The universal HBV vaccination of new-borns undertaken in most nations over the last 3 decades and effective HBV antiviral treatments (nucleos(t)ide analogue with high genetic barrier to viral resistance) introduced in the last decade have shown their beneficial effects in inducing a clear reduction of HBV endemicity in the countries where they have been extensively applied. Great hopes are now placed on new antiviral and immunotherapeutic drugs that are now at an advanced stage of study. It is in fact already conceivable that the synergistic use of new drugs targeting more than one HBV-lifecycle steps (covalent closed circular DNA destruction/silencing, HBV entry inhibitors, nucleocapsid assembly modulators targeting viral transcripts) and of some new immunotherapeutic agents might eliminate the intrahepatic covalent closed circular DNA and achieve the eradication of HBV infection. In spite of this, a strong effort should be given to extensive educational and screening programs for the at-risk population and to the implementation of HBV vaccination in developing countries.

Key words: Hepatitis B virus; Chronic hepatitis B infection; Hepatitis B virus prevention; Vaccination

Core tip: The spread of hepatitis B virus (HBV) infection has recently decreased in several countries due to the universal HBV vaccination of new-born babies and to the extended use of HBV nucleos(t)ide analogues with high genetic barrier to viral resistance. However, HBV vaccination and extensive educational and screening programs for at risk populations should be implemented predominantly in developing

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countries. New drugs targeting more than one HBV-lifecycle steps and of some new immunotherapeutic agents are under investigation with the aim of obtaining the clearance of hepatocytic covalent closed circular DNA through their synergistic action.

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INTRODUCTION

Despite the universal vaccination campaigns against hepatitis B virus (HBV) undertaken in most nations over the last 3 decades, HBV is still a global health problem with about 257 million people chronically infected, at least 40% of world population being an HBV contact or carrier[1]. About half million deaths per year are due to complications of advanced chronic hepatitis, and 340000 are due to hepatocellular carcinoma (HCC)[2,3].

The level of HBV endemicity, evaluated on the prevalence of subjects with HBV chronic infection, varies significantly from one country to another and in some countries from one geographic area to another. The rate of hepatitis B surface antigen (HBsAg) chronic carriers ranges from 0.5% to 2% (low endemicity) in most countries of North and South America, Western and Central Europe, Australia and northern Africa, from 2.1% to 8% (intermediate endemicity) in most eastern European and central Asian nations and above 8% (high endemicity) in some eastern Asian and sub-Saharan African countries and in Alaska[4,5]. Ten HBV genotypes (HBV-GT) have been identified at present, and their geographical distribution is of great epidemiological interest because it is conditioned by both local diffusion and migratory flows[4-8]. HBV-GT-A predominates in North America, eastern Africa and northern/western Europe[9,10], HBV-GT-B and -C in Asia[11], HBV-GT-D in countries facing the Mediterranean sea[11-21], in the Middle-East and in southern Asia[5], HBV-GT-E in central-western Africa[4,19,22], genotype F in southern and central America[5], HBV-GT-G in France and in some region in the United States[5], HBV-GT-H in Latin America[5] and HBV-GT-I and -J in eastern Asia[5,10]. However, several cases of acute hepatitis related to HBV-GT typical of geographic areas with high or intermediate endemicity have occurred in western countries hosting migrant populations from those areas[6,23-32].

Promiscuous unprotected sexual activity is a main risk factor for acquiring HBV infection worldwide, while other main risk factors have a different impact in different geographical areas. In fact, HBV infection is most frequently acquired at birth from hepatitis B e-antigen (HBeAg) positive mothers or through household contacts in early childhood in countries with intermediate/high endemicity, with a high rate of progression to chronicity that helps to maintain the high levels of endemicity. On the other hand, in countries with low HBV endemicity like Western Europe, North America and Australia, the major risk factor for acquiring HBV infection is the sharing of needles and other equipment between intravenous drug users[33,34], which causes the infection to remain confined to this at-risk population.

Acute Hepatitis B onset occurs 45-180 d after HBV has been acquired with some constitutional symptoms followed by dark urine and jaundice in less than 10% of children aged less than 5 years and in more than 50% of adults. The symptomatic phase of the illness lasts about 15 d and even longer in adults. Immune-complexes related extrahepatic manifestation (membranous glomerulonephritis, necrotizing vasculitis and papular acrodermatitis) are rare events[35,36].

Fulminant hepatitis is due to an overreaction of the immune system; it develops in about 1% of the patients[37,38], leading to death in about three-quarter of them and requiring liver transplantation. The age-related difference in the clinical outcome of acute HBV infection is striking[39]. In fact, more than 95% of adult patients spontaneously recover and develop a long-lasting immunological protection against reinfection, provided by seroconversion to hepatitis B surface antibody (anti-HBs) and by cellular immunity, while only 2%-5% progresses to chronicity[40]; instead, 90% of new-borns and 30% of children aged 1-5 years progresses to chronicity[41]. The difference in the outcome between children and adults is based on the degree of

reactivity of the cellmediated immunity, recognized as the true engine for eliminating HBV infection, low in new-borns and children and normal or high in teenagers and adults[42]. Risk factors for a more severe clinical course have been recognized in being a young adult or of female sex, in coinfection with hepatitis D virus (HDV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV), in alcohol abuse and in intravenous drug use[43-53].

Once a patient has recovered and serum HBsAg cleared, a residual HBV replication persists, as evidenced by the detection of small amount of HBV-DNA inside the hepatocytes, a virologic condition named occult B infection[54-63].

Depending on the entity of HBV replication and on the effectiveness of the immune-response, chronic infection has a variable clinical presentation broadly grouped in either an asymptomatic stable HBsAg carriage, chronic hepatitis or liver cirrhosis with or without HCC[23,64,65]. Patients with chronic hepatitis progress to cirrhosis at a rate of 1%-5% per year[66]; and, in turn, HBV cirrhotic patients develop HCC at a median rate of about 3.7% per year[24,67-70].

The wide spread of HBV infection, its frequent evolution into chronicity with the possibility of developing liver cirrhosis and HCC and its progression to death in patients who do not undergo a successful liver transplantation have called for extensive HBV vaccination campaigns and effective therapeutic measures.

USE OF HBV VACCINATION IN REDUCING THE SPREAD OF HBV INFECTION

Introduced in 1982, HBV vaccination is the most effective measure to prevent HBV infection[71]. One dose of the currently used HBV vaccine contains 5 μg of recombinant HBsAg produced in in yeast *Saccharomyces cerevisiae* with recombinant DNA technology and adsorbed on amorphous aluminium sulphate hydroxyphosphate. Hepatitis B vaccine is given as a three-dose series. Post-vaccination testing is required, and a person with suboptimal response (serum titters of antibody to HBsAg < 10 mIU/mL), like immunocompromised persons and those with advanced renal disease[71], should receive a fourth dose or be revaccinated[71-75]. HBV vaccination provides a protective production of antibody to HBsAg > 10 mIU/mL in about 95% of subjects and is more effective in children and young adults than in adults over 40. In adults, about 90% reach anti-HBs protective levels, and females respond to HBV vaccine better than males[76,77]. It has also been documented that vaccine induced anti HBV immunity lasts at least 3 decades[78-81] and is presumably life-long.

HBV vaccination had been initially recommended for infants born to HBV-infected mothers and for adults at risk for acquiring HBV infection (sexual partners or household contacts of HBsAg-positive persons, subjects with more than one sexual partner, males having sex with males; injection drugs users; incarcerated persons; health care workers and public safety employees at risk for exposure to blood or blood-contaminated body fluids; adults with diabetes mellitus; persons with advanced renal disease, persons with chronic liver disease not HBV-related, pregnant women who are at risk during pregnancy, HIV-infected persons; international travellers to regions with high or intermediate levels of HBV endemicity and any adult seeking protection from HBV infection)[71-73]. HBV vaccination offered to young or adult subjects at risk of infection has not been particularly effective, since it is estimated that only 20%-30% of those in need have accepted vaccination, and, consequently, no evident reduction in HBV endemicity has been obtained. Worthy of mention, the prevalence of acceptance of HBV vaccination in healthcare workers (HCWs) ranges from 15% in African countries to nearly 75% in the United States[82-87]. In addition, half of HBV vaccinated subjects completed the vaccination schedule, resulting in a lower production of anti HBs and, consequently, in a risk of lower level and lower duration of protection. Several reasons contribute to the poor acceptance of a necessary vaccination, like little information on the usefulness or effectiveness of the vaccine, poor confidence in its effectiveness, fear of adverse reactions, lack of availability and cost of vaccine in some countries[88-91]. That being the case, countless decades would have been necessary to reach the worldwide eradication of HBV infection.

A more effective vaccination strategy was therefore chosen in most countries. The universal vaccination of all new-born babies has shown beneficial effect wherever it has been correctly applied, with a clear reduction of the levels of HBV endemicity. Worthy of mention, prior to the introduction of the national HBV vaccination program in 1984, approximately 15%-20% of the Taiwanese adult population were HBsAg positive[92,93]. The effectiveness of this program was demonstrated by the significant decrease in the incidence rate of HBV chronic carriers and the rate of

mother-to-child HBV vertical transmission[94-98]. An example of this favourable effect is the strong decrease in the rate of HBsAg positivity in university students of this country, which was decreased from 9.7% in those born before 1974 to less than 1% in those born after 1992[99].

After an 8-year application of universal HBV vaccination of new-borns in Saudi Arabia, the HBsAg prevalence in children aged 1-12 years dropped from 6.7% in 1989 to 0.3% in 1997[100]. In Gambia, a clear reduction in newly acquired HBV infections, HBsAg carrier rate and HBV-related mortality was observed 14 years after the introduction of HBV vaccination in children[101]. Also, in Alaska, the implementation of HBV vaccination induced a decrease in the HBsAg carrier rate[102].

The impressive reduction in HBV endemicity in countries where universal vaccination against HBV has been applied is in stark contrast to the persistence of high HBV endemicity persisting in developing countries where HBV vaccination programs have been poorly applied. An example of this contrast was recently observed by us in a cohort of migrants who came from countries of sub-Saharan western Africa to Europe. In this cohort, migrants born in western African countries where HBV vaccination has been not sufficiently applied showed an HBsAg positivity ranging from 9.7% to 22.5%, whereas those born in Nigeria showed the beneficial effects of a universal HBV vaccination of new-borns well applied from 2 decades. Those from Nigeria had a global rate of HBsAg positivity of 4.1% and age-related rates of 3.5% in subjects less than 25 years, 4.1% in those aged 26-40 years and 17.9% in those aged over 41, a cohort effect underscoring a tendency of HBV endemicity towards reduction.

Concluding on this point, there remains much to be done to get a proper extended application of all the possible prophylaxis measures aimed at reaching the eradication of HBV infection. Firstly, HBV universal vaccination programs of new-born babies should be extensively applied and never discontinued in all world countries. Secondly, extensive information campaigns will have to be undertaken so that people at risk of HBV infection may receive instructions on how this infection spreads and how to prevent it and then be encouraged to undergo screening and, if exposed to infection, to HBV vaccination[103]. Thirdly, a permanent program of screening and vaccination of migrants from areas of intermediate or high endemicity must be applied in all host nations. These remedies, however, will not be enough as there are, as of now, some hundreds of millions of infected subjects able to transmit the infection worldwide.

Mainly due to individual factors (*e.g.*, immunogenetic conditions, advanced age, obesity, smoking or chronic diseases such as celiac disease, diabetes, HIV infection, advanced kidney disease, autoimmune diseases), 5%-10% of the adult population does not respond or responds insufficiently to anti-HBV vaccine (anti-HBs titres < 10 mIU / mL). For non-responders, the pathway to improve the immunogenicity of the vaccine adjuvant has been followed and an oligonucleotide of the cytosine phospho-guanosine, a Toll-like 9 agonist receptor potent stimulator of the vertebrate innate immune system, has been used as an adjuvant for a recombinant two-dose hepatitis B vaccine (administered at wk 0 and 4). Recently approved for use in adults, initial data have shown a higher percentage of protected subjects compared to alum-adjuvanted vaccines[71,73,74,79,81].

USE OF THE ANALOGOUS NUCLEOS(T)IDES IN ABOLISHING THE INFECTIVITY OF HBV CHRONIC CARRIERS

The pharmacological suppression of HBV replication in HBV chronic carriers is another opportunity for health authorities to undertake an effective path towards the eradication of HBV infection. Although a sustained eradication of intrahepatic covalent closed circular DNA (cccDNA) as well as integrated cccDNA is currently not feasible, long term suppression of viral replication with HBV DNA serum clearance may be easily obtained with long-term administration, maybe life-long, of high genetic barrier to resistance nucleos(t)ide analogues tenofovir disoproxil fumarate (TDF), entecavir (ETV) or tenofovir alafenamide (TAF). These drugs have improved the outcomes of HBV-related chronic hepatitis by lowering the rate of transition to liver cirrhosis and reducing the risk of HCC development, but the clearance of serum HBsAg is only achieved in a small portion of treated patients[104].

Treatment with interferon in its pegylated form (PEG-IFNα), extensively used as monotherapy in the past, will become obsolete because of its poor efficacy and of the frequent occurrence of badly endured and sometimes severe adverse reactions during long-term treatment. In HBsAg/HBeAg positive patients, the seroconversion to anti-

HBe was obtained only in 29%-32% of patients after 1-year PEG-IFN treatment and to anti-HBS only in 3%-5%[105,106]. In HBeAg-negative patients, a favourable response with stable normalization of serum alanine aminotransferase and serum HBV DNA reduced below 400 copies/ml was obtained only in 15% of cases treated for 12 mo, with HBsAg loss in about 4%[107].

The first generation nucleos(t)ide analogues lamivudine, adefovir and telbivudine have become obsolete because their low genetic barrier is unable to prevent the formation of viral resistant strains. In addition, the sequential use of ETV to treat lamivudine resistance increases the risk of ETV resistance. A switch to tenofovir has been demonstrated to be effective in patients with confirmed lamivudine, telbivudine, adefovir or ETV resistance.

Long-term therapy with nucleos(t)ide analogues with high genetic barrier to viral resistance (ETV, TDF) is required to obtain a stable suppression of HBV replication[108]. These drugs are highly recommended as first-line therapy because HBV resistance is a rare event in nucleoside-naïve patients during a 5-year treatment with ETV and no resistance with a 7-year treatment with TDF[109]. Histological evaluation after a long-term treatment with ETV or TDF showed an impressive improvement in liver necroinflammation and fibrosis scores in most patients[110,111]. In addition, compared with controls, a significant reduction in the incidence of HCC has been observed in HBsAg positive cirrhotic patients undergoing a long-term therapy with ETV or TDF[112-117].

A 5-year ETV treatment induced HBV DNA serum clearance in more than 90% of HBeAg positive patients with chronic hepatitis[118], and a similar rate was obtained with TDF[109]. Seroconversion to anti-HBe was obtained in about 20% of patients after 1-year of ETV or TDF therapy[118,119].

HBsAg loss occurred in 11.8% of HBeAg-positive patients after 7 years of TDF treatment, more frequently in Caucasians than in Asians[109]. Consolidation therapy is recommended after the loss of HBsAg[120].

TAF is an oral second-generation prodrug of TDF with a high genetic barrier to viral resistance. Although TDF and TAF show similar rates of cure[121-123], switching from TDF to TAF provides improvement in bone density and renal function, a favourable effect in a log-term treatment[124,125].

Currently, new drugs are being tested that are aimed at eradicating chronic HBV infection: HBV entry inhibitors, capsid inhibitors, short interfering RNA and targeting cccDNA[126-132]. Briefly, a blockade of HBV entry in experimental cells was obtained using a pre-S acylated peptide of the large HBsAg protein, and further studies on chronic HBV and HDV infection are ongoing[133]. In some experimental models it has been shown that the AB-423 capsid inhibitor is able to direct erroneously capsid assembly to inhibit pregenomic RNA encapsidation and consequently to reduce cccDNA concentrations in liver cells[128-138].

Several antisense short interfering RNAs targeted towards HBsAg transcripts have achieved mRNA degradation in pre-clinical or clinical evaluation. Among these, ARC 520 is of interest. It is directed towards HBV RNA transcripts and reduces the synthesis of HBV DNA and viral proteins[138]. Regarding cccDNA targeting, several DNA cleavage enzymes have been tested in experimental models and preliminary data seem encouraging[132].

In addition, experimental studies are underway to develop new drugs or therapeutic vaccines that may regulate the immune-system dysfunction in hepatitis B[139-150].

CONCLUSION

The universal HBV vaccination of new-borns has produced significant results in countries where, responding to the demand of the World Health Organization, it has been correctly applied. Nevertheless, in several developing countries, socio-economic reasons have impaired the application of HBV vaccination, delaying the achievement of a global reduction in HBV endemicity. Also, the vaccination on a voluntary basis of adults at risk of HBV infection has failed to contribute to the project of a progressive reduction of the levels of endemicity. This being the case, we believe that an additional 2-3 decades of extensive application of the universal HBV vaccination will be needed to achieve a substantial reduction of HBV spread.

Another aspect of the ambitious project to eradicate HBV infection is the extensive information campaign on how to acquire the infection and how to prevent it. So far, information campaigns have been occasional and limited to certain risk categories in many countries and therefore have not substantially contributed to the reduction of HBV endemicity.

Good news comes from the therapeutic management of chronic hepatitis B. In fact, the new nucleos(t)ide analogues (ETV, TDF and TAF) that effectively suppress HBV replication may be used for a very long period with no risk to induce viral resistance. In addition, new drugs for the complete eradication of HBV replication, thus ensuring a complete cure, are currently being developed and will be very likely be available in the next decade.

The set of data reported here suggests that prolonged extended application of the universal HBV vaccination of new-borns and the utilization of the high genetic barrier to resistance nucleos(t)ide analogues and, in the near future, of some drugs today in experimental development will allow for, in the next 2-3 decades, a strong reduction of HBV endemicity and possibly the eradication of HBV infection.

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