Review article

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Hepatitis B vaccination and immunotherapies: an update

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World Health Organization (WHO) estimates that 257 million people were living with chronic hepatitis B virus (HBV) infection. Highest HBV prevalence was found in the WHO Western Pacific Region (6.2%) and in the WHO African Region (6.1%). The HBV vaccine is the best protection against chronic HBV infection and its complications. Globally, routine infant immunization against HBV has increased with an estimated coverage of 84% in 2017. Nevertheless, in many countries further efforts are needed to implement this coverage and ensure national immunization programs for people at major risk for HBV infection. Therapeutic vaccination in chronic HBV infected patients can cause anti-HBV immune responses able to remove and/or cure infected hepatocytes. It shows promising results in murine model and human trials, but these results need to be consolidated by further multicenter clinical studies. In particular, the efficacy of therapeutic vaccine seems to improve by combination therapies.

Keywords: Hepatitis B virus infection, Vaccination, Therapeutic vaccine, Chronic hepatitis B

Introduction

In 2015, World Health Organization (WHO) estimates that 257 million people were living with chronic hepatitis B virus (HBV) infection (defined as hepatitis B surface antigen [HBsAg] positive) [1].

The highest prevalence of HBV infected population was found in the WHO Western Pacific Region (6.2%) and the WHO African Region (6.1%). The HBV prevalence was estimated of 3.3% in the WHO Eastern Mediterranean Region, 2.0% in the WHO South-East Asia Region and 1.6% in the WHO European Region. The lowest prevalence of HBV infected population (0.7%) was found in the WHO Region of the Americas [1].

HBV infection is transmitted through contact with the blood or other bodily fluids of an infected person. Unsafe sex could put people at risk, as could getting a tattoo, piercing or manicure/pedicure in places with inadequate hygienic standards of utensils such as clippers and scissors. The HBV infection can cause serious health problems such as liver cancer, cirrhosis and liver failure resulting in death [2].

In 2017, the European Union and European Economic Area Member States reported 26.907 cases of HBV infection, of whom 9% were reported as acute, 58% as chronic, 32% as 'unknown' and 1% could not be classified [3]. In the WHO European Region an estimated 13.3 million people live with chronic HBV infection (1.8% of adults) [4].

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The people at higher risk for contracting infection are people who frequently require blood or blood products, dialysis patients and recipients of solid organ transplantations; people who inject drugs; inmates; household and sexual contacts of people with chronic HBV infection; people with multiple sexual partners; healthcare workers; travelers in endemic areas who have not completed their HBV vaccination. All of these groups should be vaccinated [1].

Several studies showed that the prevalence of HBV infection in prisoners ranged from 1.4% to 23.5%. In fact, the highest prevalence of HBsAg was found in prisoners of West and Central African (23.5%). High levels of chronic HBV infection have also been reported in Eastern and Southern Africa (5.7%) and in Eastern Europe and Central Asia (10.4%). The lowest prevalence was found in North America (1.4%) [5].

The results of an Italian study [6], involving a total of 57 detention facilities, showed a HBV prevalence of 2.0%. This prevalence was calculated on 15,751 inmates enrolled in this study, out of 17,086 inmates. For this study was designed a specific clinical record and all diagnoses were considered according to the International Classification of Diseases, Ninth Revision, Clinical Modification. The study showed that the prevalence of patients with chronic HBV infection is probably underestimated by the National Health Service, compared to that emerged from seroprevalence studies.

A cross-sectional screening study was conducted in Italy through the evaluation of serum markers for HBV infection (presence of HBsAg) in prison. The study identified 4.4% of HBsAg-positive subjects, of whom about 35% of foreigners [7]. Geue et al. [8] in a systematic review evaluated 15 studies concerning HBV screening on 2,284 initially considered. The authors found the dissimilarity between the different population groups examined, in particular some populations studied in the past (such as the general population) should not be screened in the future as the screening results not cost-effective. On the contrary, existing evidence suggests that screening activity in migrant populations could be a good cost-effective strategy. This result does not show changes based on the use of different economic models adopted, the evaluation of the quality-adjusted life years, the years of life gained, the number of cases detected, and the number of infections avoided.

Based on the clinical and public health relevance of HBV diffusion, the review will examine and discuss the new important strategies of HBV prevention and control by vaccination and the innovative vaccine therapy in chronic HBV patients.

The anti-hepatitis B virus vaccination

The vaccine against hepatitis B is the best protection against chronic HBV infection and its complications, and it is included in routine childhood vaccinations in many countries. The vaccine against HBV has been available since 1982 and became widely available after the year 2000, therefore the adults of today may not have been vaccinated as children. The vaccine is extremely effective, and three doses give immunity for at least 20 years. The vaccine has greatly reduced the prevalence of HBV and the socioeconomic impact in industrialized countries.

WHO recommends that all infants receive the vaccine against HBV as soon as possible after birth, preferably within 24 hours. Routine infant immunization against HBV has increased globally with an estimated coverage (third dose) of 84% in 2017. The low prevalence of chronic HBV infection in children under 5 years of age, estimated at 1.3% in 2015, can be attributed to the widely use of vaccine against HBV [1].

In Europe routine childhood vaccination is included in 20 (74%) of the 27 countries (Belgium, Bulgaria, Czech Republic, Cyprus, Estonia, France, Germany, Hungary, Italy, Malta, Latvia, Luxembourg, Portugal, Romania, Slovakia, Slovenia, Spain, Poland). In 12 (60%) of these countries, namely Belgium, Cyprus, Estonia, France, Germany, Italy, Malta, Latvia, Romania, Poland, and Luxembourg, vaccination is planned not only in childhood but also in older children and in adolescents. Six countries have not yet introduced universal immunization against hepatitis B: Denmark, Finland, Iceland, Norway, Sweden, and United Kingdom. They have very low endemicity and consider hepatitis B to be a limited public health problem, thus not justifying additional expense [9].

In Italy vaccination, starting in 1991, is planned for all newborns who must undergo mandatory vaccination. Until 2003 (12 years after the law came into effect), adolescents were also vaccinated during the 12th year (the population born after 1979 received anti-HBV vaccination at the age of 12 years starting from 1991) [10].

Vaccination for people at higher risk for contracting hepatitis B virus infection

The Centers for Disease Control and Prevention highlighted the importance of blood screening for HBV and subsequent anti-HBV vaccination in the prison population for all people who received a medical evaluation in prison, unless they have

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of a proof of completion of the vaccination series or serological tests of immunity from infection [11]. Although vaccination against HBV has been recommended in prisoners since 1982, when the vaccine was made available, only a few countries usually vaccinate prisoners [7]. In Italy, a ministerial decree in October 1991 recommended vaccination against HBV in people at risk, including prisoners. Vaccination is currently recommended at months 0, 1, and 2 and again in month 6.

For those who are homeless, there is an accelerated calendar for immunization against HBV (0, 7, and 21 days) with a booster at 12 months, which results in a higher level of completion and seroconversion rates than traditional programs [12].

One of the main reasons for why inmates are not vaccinated is the lack of adherence to the screening program by prisoners. The reasons for non-compliance are probably attributable to both personal and institutional aspects such as lack of knowledge and awareness (perceived risk) regarding viral hepatitis and transmission routes, lack of motivation and/or awareness of the procedure, the fear of stigma by prison staff and colleagues, but also the lack of proactive strategies on the part of the staff and, not least, the lack of continuity of care after being released from prison.

Van Herck et al. [13] have shown that an accelerated program (0, 1, 2, and 12 months) or a super-accelerated program (0, 7, 21 days, and after 12 months) can lead to a faster response and increase in levels of anti-hepatitis B surface (HBs) antibodies ≥10 IU/L. For the rapid seroconversion and the immediate protection in the short term, it is necessary to use the most accelerated program for groups at major risk of infection. Since no long-term protection data have been reported for these more accelerated programs, a fourth dose per month is still needed 12. Stasi et al. [14] evaluated 1,075 subjects screened for HBV serum markers, 67.9% were susceptible to infection and needed to be vaccinated, of these 82% agreed to be vaccinated. Five hundred and fifty-five inmates (95.1%) received the first vaccine dose, and 404 (83%) underwent the third dose at day 21.

Almasio et al. [12] recommended vaccination against HBV in immigrants belonging to the following categories: coming from highly endemic areas, drug addiction, non-immunized prisoners, partner of an infected person, and patients with chronic liver disease not related to HBV. In particular, for all these groups an accelerated vaccination should be offered to allow a sufficiently high compliance rate and avoid dropouts.

Wright et al. [15] highlighted for homeless subjects the importance of an accelerated vaccination schedule (0, 7, 21 days) with a booster at 12 months that results in higher completion rates and similar seroconversion rates compared to traditional schedules.

Wouters et al. [16] studied a highly mobile at-risk population of commercial sex workers in Belgium, and demonstrated that a 0-, 1-, 4-month schedule is easier to offer and confer equal protection within a shorter period of time. Mangen et al. [17] evaluated the cost-effectiveness of the decentralized targeted vaccination program against HBV for behavioral high-risk groups conducted by regional public health services in the Netherlands since November 1, 2002. Target groups for free vaccination were men having sex with men, commercial sex workers, and hard drug users. Heterosexuals with a high partner change rate were also included until November 1, 2007. The authors concluded that HBV-vaccination program is a cost-effective intervention in certain unvaccinated high-risk adults, and was a good alternative to national immunization programs. In the Netherlands, HBV vaccination was only introduced in the national immunization programs in 2011.

The US Preventive Services Task Force made recommendations screening for HBV infection in pregnant women at their first prenatal visit [18].

In line with international guidelines on HBV vaccination in human immunodeficiency virus (HIV)-infected population [19,20], a recent review by Catherine and Piroth [21] highly recommended vaccination against HBV, based on currently available data regarding HBV vaccination in people living with HIV, according to their main characteristics and their vaccine and therapeutic background. Response to vaccination is defined by a seroconversion with anti-HBs antibodies >10 IU/mL. In particular, double-dose rescue vaccination with at least three doses appears to induce better immunization against HBV in HIV-infected populations and an annual supervision of anti-HBs antibodies titers are recommended to monitor when new boosters are required.

Beyond the current therapy for chronic hepatitis B virus infection

The WHO guidelines for HBV prevention, care and treatment recommended treatment in all adults, adolescents, and children with chronic HBV infection with compensated or decompensated cirrhosis regardless of alanine aminotransferase (ALT) levels, hepatitis B e antigen (HBeAg) status, or HBV

DNA levels [22]. Treatment is recommended for adults with chronic HBV infection who do not have clinical evidence of cirrhosis, but who are over the age of 30 years and have persistently abnormal ALT levels and high level of HBV replication (HBV DNA >20,000 IU/mL), regardless of HBeAg status. These guidelines are based on a public health approach and they considered feasibility and effectiveness in countries with limited resources.

The current potent antiviral agents such as tenofovir and entecavir cause minimal risk of resistance, the viral suppression is over 99% and present very high rate of tolerability. Several lines of evidence suggest that long-term complete suppression of HBV replication by nucleosides/nucleotides (NUC) results in improved long-term outcomes such as the reduced risk of developing liver cirrhosis, hepatocellular insufficiency and hepatocellular carcinoma [23,24] and histologically proven regression of liver fibrosis [25]. The disadvantages include the unlimited duration of treatment, the low rate of loss of HBsAg and the seroconversion to anti-HBs. Moreover, NUCs are still not able to eradicate the cccDNA.

HBV drugs are also currently being trialled, which induce persistent suppression of HBV-DNA, HBsAg negativity and eradication of cccDNA. Interferon induces both the immunomodulation and suppression of cccDNA transcription, but antiviral drugs target different steps of the HBV life cycle are also in development. These drugs are being tested which target the cccDNA, including inhibitors of the formation of cccDNA, transcription inhibitors and drugs that disrupt or degrade the cccDNA [26]. Other drugs still undergoing testing include translocation inhibitors of the virus in the cytoplasm or assembly of the nucleocapsid to DNA [27], or inhibitors of the release of HBsAg [28].

Finally, new immunomodulators are in a more advanced trial stage. Among these are HBV-specific immunomodulators and the anti-programmed cell death protein 1 and therapeutic vaccines which boosts the immune response.

Vaccine therapy for chronic hepatitis B virus infection

A complex interaction between virus and host causes HBV persistence with suboptimal immune responses, such as malfunctioning of cell-mediated immunity and dendritic cell and imbalance of cytokine production [29].

The therapeutic vaccination in chronic HBV infected patients can cause anti-HBV immune responses to remove and/or cure infected hepatocytes without host cell damage, with subsequent prevention of viral spread to new hepatocytes and long-term viral control [30]. These approaches for stimulating T-cell responses with therapeutic vaccination include the use of different vaccination doses and frequencies and prime-boost; the use of DNA or peptide vaccines, vector or cell-based vaccines, and finally the use of a combination of core, X and polymerase antigens in addition to HBsAg [30,31].

One of the firsts clinical study on HBV vaccine therapy was carried out on 32 consecutive chronic HBsAg carriers with chronic hepatitis and detectable HBV DNA received three standard doses of the GenHevac B vaccine at one month intervals. Six months after the first dose, 12 patients (37.5%) had undetectable HBV DNA while three others showed significant decrease in HBV DNA titers. Eight of these 15 responders received a standard course of α-interferon and all still had undetectable HBV replication. Among 17 non responders to vaccine, 13 received α-interferon, and only three stopped HBV replication. In conclusion, 53% of HBV patients achieved undetectable HBV DNA [32]. Recently, Lai et al. [33] enrolled 20 chronic HBV infected e antigen-negative patients, with HBsAg <1,000 IU/mL. Seven vaccine doses were administered every 8 weeks and HBsAg levels and anti-HBs were longitudinally monitored until 48 weeks post-vaccination. In these patients, the vaccination resulted in significant HBsAg decline.

Bian et al. [34] investigated whether preS1-polypeptide vaccination is a potential treatment for chronic HBV infected patients. They found that the preS1 domain of L-HBsAg presents strong immunogenicity for both B-cell and T-cell responses. Moreover, the anti-preS1 induced by preS1-polypeptide cleared HBV DNA in carrier mice and blocked HBV infection/reinfection to hepatocytes, suggesting that the subsequent vaccination with HBsAg could induce anti-HBs seroconversion in HBV carrier mice.

In a phase I clinical trial, Zoulim et al. [35] studied safety, immunogenicity and efficacy of TG1050 in chronic HBV infected patients. TG1050 is an adenovirus 5-based vaccine that expresses HBV polymerase and domains of core and surface antigen. This study included two sequential phases: one single dose cohort and one multiple doses cohort. TG1050 was well tolerated in both cohorts and in association with NUC induced HBV-specific cellular immune response.

In a phase II clinical trial, Boni et al. [36] assessed the efficacy and safety of GS-4774 in viremic HBV infected patients. All of these patients received tenofovir disoproxil fumarate with or without GS-4774. GS-4774 is a yeast-based therapeu-

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tic vaccine containing.

HBV S, X, and core proteins. In murine model and cells from chronic HBV infected patients, GS-4774 induced interferon-γ-producing CD4+ and CD8+ T cells [37]. Boni et al. [36] found that vaccination can increase production of interferon-γ, tumor necrosis factor, and interleukin 2 by CD8þ T cells exposed to antigenic peptides, with little effect on CD4þ T cells and they concluded that GS-4774 might be used in association with other antiviral treatment to boost the immune response.

In phase III clinical trial, Al Mahtab et al. [38] studied the efficacy of a therapeutic vaccine (NASVAC) containing both HBsAg and hepatitis B core antigen versus pegylated interferon in a total of 160 chronic HBV infected patients. In this study, the viral load significantly decreased in NAVASC group compared to pegylated interferon-group at 24 weeks of follow-up. Clearance rate of HBeAg was also more frequent in NASVAC group compared to pegylated interferon, but a slight progression into cirrhosis was found in NASVAC group compared to pegylated-IFN group. Brillanti et al. [39] in a pilot study randomly assigned five patients with HBeAg-negative chronic HBV infection to receive HBV vaccine therapy: three doses, 1 month apart, of 40 mcg yeast derived recombinant hepatitis B vaccine (HBVAXPro), while five patients continued nucleos(t)ide analog therapy without vaccination. HBsAg and HBV DNA status was assessed 6 months afterwards. In HBVAXPro group the vaccine therapy enhanced HBsAg loss and anti-HBs seroconversion.

Conclusion

The HBV vaccine is the best protection against chronic HBV infection and its complications. Globally, routine infant immunization against HBV has increased with an estimated coverage of 84% in 2017, but further efforts are needed to implement this coverage in many countries and ensure national strategies for people at major risk of contracting HBV infection. Severe lines of evidences indicate that therapeutic vaccine has promising results in murine model and human trials, but these results need to be consolidated by further multicenter research clinical studies. In particular, the efficacy of therapeutic vaccine able to enhance T-cell responsiveness seems to improve by combination therapies.

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