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Expectations for Hepatitis B Universal Vaccination for Hepatitis B Virus Eradication

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Abstract

Context: To control hepatitis B virus (HBV) infection, we discuss in this review the expectations for a universal vaccination to eradicate HBV from the perspective of preventing hepatocarcinogenesis and hepatitis due to HBV. HBV infections are broadly classified into "acute infection" and "persistent infection" (HBV carrier state). Most adults who acquire HBV will only experience the "acute infection" that eventually heals, while nursing infants without adequately developed immune function and adults with immune dysfuncstion who contract HBV will be unable to eradicate the virus and will thus develop the "persistent infection." Hepatitis B virus is difficult to treat, but is simple to prevent through means such as vaccination. However, hepatitis B universal vaccination was not performed through 2014 in Japan.

Evidence acquisitions: The relevant English and non-English published papers were searched using online databases of PubMed, ISI Web of Science, SCOPUS, Science Direct and EMBASE from January 1985 to April 2015. We summarized the findings of 28 relevant studies in this review.

Results: In response to the demand for universal vaccination, the Immunization and Vaccination Committee of the Health Sciences Council decided to implement universal vaccination of HBV for newborns because in January 2015 confirmation was reached of the horizontal infection of HBV in children and the effectiveness of vaccination in different genotypes.

Conclusions: In this review, we discuss the expectations for hepatitis B universal vaccination for hepatitis B virus eradication.

Keywords

Hepatitis B universal vaccination, Antiviral treatment, Hepatocellular carcinoma

Abbreviations

HCC: Hepatocellular Carcinoma, HBV: Hepatitis B Virus, CHB: Chronic Hepatitis B, HBV: Hepatitis B Virus, HBsAg: Hepatitis B Virus Surface Antigen, Nucleos(t)ide: Nucleoside/Nucleotide; HBeAg: hepatitis B Virus Envelope Antigen

Introduction

The incidence of hepatitis B virus (HBV)-related HCC has not declined for the past several decades. HBV is essentially a disease that could potentially be eradicated by a vaccine. According to the World Health Organization (WHO), two billion people (one-third of the global population) have been infected with HBV worldwide, and more than 240 million are chronic carriers (4–6% of the world population) [1].

On the other hand, hepatitis C virus (HCV) is the leading infectious disease in Japan, but due to therapeutic advances, sustained viral response rates (SVRs), even among patients with refractory liver disease, have improved to 80–90% [2]. Therapeutic response is particularly good [3-5], even among the elderly and patients with progressive hepatic fibrosis, who are at very high risk for HCV-related hepatocellular carcinoma (HCC). Even after HCC treatment, interventions involving aggressive antiviral therapy can yield improved survival [6-8], suggesting that HCV-related HCC may be finally eradicated in the future.

This review examines vaccination strategies, the current status of HBV infection, and unresolved issues related to controlling HBV infection. We discuss the expectations for a universal vaccination (i.e., a vaccine available to all citizens) to eradicate HBV from the perspective of preventing hepatocarcinogenesis and hepatitis due to HBV.

Epidemiology of Hepatitis B

Of the approximately 240 million people worldwide who are said to be infected with HBV, 10–15% have refractory liver disease in the form of chronic hepatitis, cirrhosis or HCC. Each year 600,000 people die from diseases caused by HBV infection, such as cirrhosis and HCC [9].

In Japan, approximately 1.3–1.5 million people (about 1% of the population in Japan) are estimated to have persistent infection, and there are currently an estimated 1,800 new inpatients with acute hepatitis B each year. When including mild and latent forms of the disease, the number of estimated new cases of infection exceeds 5,000 per year. In any event, HBV infection has the potential to progress from chronic hepatitis to cirrhosis, and even to HCC.

Infection with Hepatitis B Virus

HBV infections are broadly classified into "acute infection" and "persistent infection" (HBV carrier state). In "acute infection," the virus is removed from the body after a certain period following establishment of infection, and the hepatitis B viral infection is cured.

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Clinical features of acute infection typically consist of inapparent infection that heals without any subjective symptoms, or apparent infection in which acute hepatitis occurs and rarely becomes fulminant. Around 400 people are estimated to develop fulminant hepatitis each year, with 40% of these cases reportedly caused by HBV [10]. The risk of these acute cases of HBV infection becoming chronic is highest in nursing infants and preschool children. In "persistent infection" (HBV carrier state), on the other hand, the virus gradually settles within the body; mainly the liver. Most adults who acquire HBV will only experience the "acute infection" that eventually heals, while nursing infants without adequately-developed immune function and adults with immune dysfunction who contract HBV will be unable to eradicate the virus and will thus develop the "persistent infection." Recently, there has been an increase in HBV genotype A infection, which is characterized by a high rate of progression from acute to chronic hepatitis, giving rise to concerns that chronic hepatitis is spreading, even among adults [11,12].

Treatment and Prevention of Hepatitis B

While treatment of acute hepatitis B virus infection usually consists of symptomatic therapy or watchful waiting, chronic hepatitis B is mainly treated with antiviral drugs (nucleic acid analogs) [13] and interferon-based virus eradication therapy. However, unlike hepatitis C therapy, in which total elimination of the virus is possible, the response rate to interferon therapy is around 30–40% [14].

Treatments for HBV such as nucleotide analogues and interferon have improved, but HBV patients are often required to receive the lifelong treatments with high cost and cure is still a challenging goal.

Hepatitis B virus is difficult to treat, but is simple to prevent through means such as vaccination. Moreover, considering the need to address mother-to-child transmission as well as the risk of horizontal transmission, universal vaccination of all nursing infants has been highlighted as one of the most crucial initiatives. In 2013, 183 of the 194 member nations of the World Health Organization (WHO) had already launched a universal vaccination program to combat hepatitis B.

Main Transmission Routes of HBV

Transmission routes of HBV to children are mainly from mothers and sexual contact is the main route of transmission for adolescents or adults recently in Japan. Horizontal transmission comprises modes of infection other than mother-to-child transmission. Other routes are varied such as blood transfusion, blood products, hemodialysis, needle treatment, a tattoo, 'needlestick' injuries, and so on [11].

In 1985, the former Ministry of Health and Welfare in Japan began the Mother-to-Child Transmission Prevention Program, and in 1986 implemented a procedure to prevent transmission from HBe/HBs antigen-positive mothers to their newborns. In 1995 the program was reviewed and expanded to prevent infection of all infants from HBs antigen-positive mothers.

The benefits of these initiatives to prevent mother-to-child transmission of hepatitis B were that infant HCC rates decreased after starting the program in 1986, leading to a significant decrease from 2001 in the incidence of HBV-related HCC compared to that of HBV-nonrelated HCC [15]. Conversely, horizontal transmission is still an issue. Although Japan has a "selective vaccination" program to prevent transmission, targeting the children of the aforementioned HBV carrier mothers, universal vaccination would not only benefit the children being vaccinated, but also could prevent the horizontal transmission described below.

Horizontal transmission comprises modes of infection other than mother-to-child transmission. Other routes are varied such as blood transfusion, blood products, hemodialysis, needle treatment, a tattoo, 'needlestick' injuries, and so on.

Previously, the most frequent form of horizontal transmission was via blood transfusion, but this has since decreased dramatically due to better screening of donated blood samples. Needle sharing has been also decreased. Today the major transmission are between family members (other than mother-to-child), via nursery schools and other public facilities, and via sexual transmitted infection (STI) in adults. A recent study found that HBV-DNA is present in the saliva, sweat, tears, urine and other bodily fluids and excretory products of carriers, such that even bodily fluids (saliva, sweat and tears) are potential sources of HBV infection [16]. Tear specimens from a child were injected intravenously into 2 human hepatocyte-transplanted chimeric mice. One week after inoculation, both chimeric mice had serum positive for HBV DNA. Strict precautions should be taken against direct contact with body fluids from HBV carriers with high-level viremia [16]. Furthermore, a study in the 1970s inoculating chimpanzees with HBe-Antigen positive serum also showed that infection through intravenous inoculation still occurred when using serum that had been diluted 100 million times [17]. These findings demonstrate the potent infectivity of HBV, and suggest that current efforts aimed only at preventing mother-to-child transmission are incapable of controlling this infectious disease.

Father-to-child transmission and associated measures

In terms of father-to-child transmission, approximately 25% of children with carrier fathers become infected and approximately 10% become carriers themselves [18]. Komatsu et al. studied transmission routes in Japan, both before and after prevention of mother-to-child transmission became possible in 1985, and discovered that father-to-child transmission was increasing relatively rapidly [19]. Unlike mother-to-child transmission, new fathers are currently not subject to screening, so introduction of a hepatitis B vaccine as universal vaccination is indispensable in addressing the issue of father-to-child infections.

Transmission via nursery schools and associated measures

It is difficult to demonstrate how HBV is transmitted at nursery schools and other facilities. Hayashi et al. investigated the extent of HBV infection in 269 children (2.9 ± 1.4 y) at 5 nursery schools located in areas in Japan known to have a high carrier rate. Consequently, 10 cases of infection were discovered, of whom 6 children had acute infection and 4 were carriers [20]. Hayashi et al. concluded that hepatitis B transmission most probably occurs among children in nursery schools where there are HBsAg carriers with HBeAg, and therefore vaccination of susceptible children is necessary [21].

Furthermore, Hayashi et al. assessed the efficacy of an inactivated hepatitis B vaccine among children in nursery schools where there was at least one hepatitis B surface antigen-positive child with hepatitis B e antigen. Of the 496 children who completed the inactivated hepatitis B vaccination protocol, 243 (aged 2.7 +/- 1.1 years) children in six of the nursery schools received three injections of the vaccine. In five other nursery schools, 253 children (aged 2.3 +/- 1.0 years) did not receive the vaccine and were used as the control group. Although nine (4.4%) of the 203 children in the control group (whom the authors were able to follow for 24 months) were infected with HBV and two of them became carriers, none of the vaccine recipients became infected. Hayashi et al. concluded that the vaccine appears to be safe, immunogenic, and efficacious in preventing HBV infection in nursery schools.

As a result of these cases, hepatitis B vaccination in nursery schools was prescribed for the first time in the "2012 Amended Guidelines for Preventing Infectious Diseases in Nursery Schools." In recent years, there has been a rise in the number of facilities where children and teachers are proactively inoculated with the hepatitis B vaccine. Expectations are now growing for a universal vaccination program as a necessary measure to combat father-to-child transmission.

Benefits and Cost Benefits of Universal Vaccination

Hepatitis B (HB) vaccines, which are the first vaccines that have been proven to prevent HCC, have played a crucial role in preventing HBV infection worldwide since their development in the 1980s. In

particular, the HB vaccines have been rapidly integrated into the national immunization programs of low-income countries since the Global Alliance for Vaccine and Immunization was launched in 2000. However, HBV has still not been eradicated.

In Taiwan, where a universal hepatitis B vaccination program was implemented as early as 1984, the virus carrier rate in children under age 5 years declined from 9.8% when the program started to 0.7% after 15 years [22]. Additionally, the mean annual incidence of HCC in children aged 6 to 14 years (per 100,000 members of the population) dropped significantly from 0.7% between 1981 and 1986 to 0.36% between 1990 and 1994 ($p<0.01$) [23]. Furthermore, Taiwan's mean infant mortality rate due to fulminant hepatitis from 1985 to 1998 (after implementation of the hepatitis B vaccination program) decreased to one third of the rate seen during 1975 to 1984 (prior to implementation) [24].

Recently, a case was reported in which two elderly Japanese patients with fulminant hepatitis B acquired HBV infection via interposal (most likely sexual) transmission during long-lasting marriages [25].

In terms of hepatocarcinogenesis, the high viral load of HBV-DNA is the most important HCC risk factor [26,27].

The need for prolonged antiviral therapy before and after HCC [28] could ultimately be perceived as a burden on the national health care expenditure. We believe that universal vaccination is currently the best way to prevent not only the onset of HBV-related hepatitis and its progression to chronic disease and HCC, but also the best way to present spread of the infection itself. Furthermore, universal vaccination is already a commonly-accepted practice around the world.

In the report of the Hepatitis B vaccine working team, the incremental total cost of HB vaccine for 1,078,000 infants (birth cohort number in 2009) was about $155 million and medical expenses for HBV related disease (acute hepatitis, chronic hepatitis, fulminant hepatitis, cirrhosis, hepatocellular carcinoma) reduction was up to about $6.3 million under universal vaccination program because of low prevalence of these disease. That means the incremental cost becomes about $148 million. As a result of cost-effectiveness analysis, incremental cost per QALY gained by HB vaccine was about $149,000 and the cost-effectiveness of universal vaccination program was not described favorable in their report in 2011. So cost-benefit is still big issue.

Conclusion

Conventional wisdom in 1985 stipulated that successful prevention of mother-to-child transmission should have allowed us to control hepatitis B in Japan. However, 30 years later, there are still no signs that HBV will be eradicated soon. Although not covered in the present study, new problems such as *de novo* hepatitis have emerged. Although there are issues surrounding cost-benefit, now might be the time to consider a shift from "selective vaccination" to universal vaccination.

In response to the demand for such universal vaccination, the Immunization and Vaccination Committee of the Health Sciences Council decided to implement universal vaccination of HBV for newborns because confirmation was reached in January 2015 concerning horizontal infection of HBV in children and the effectiveness of vaccination on a different genotype. However, there are still other issues to be resolved, such as the vaccination schedule, additional doses, catch-up vaccination, and resources. We strongly expect a smooth introduction of a HBV universal vaccination program after 2016.

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