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Current epidemiology, prevention and treatment of Hepatitis B in China

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ABSTRACT:

Hepatitis B is still the main cause of chronic liver disease in China, causing a huge burden on people's health and economic development. During the past two decades, great efforts in the prevention and treatment of hepatitis B have been made, with a lot of achievements. However, antiviral therapy for hepatitis B virus (HBV) infection and disease eradication remain a major challenge. This paper focuses on the prevalence of HBV infection and its prevention and treatment in China.

Keywords: Hepatitis B virus, Epidemiology, Prevention, Treatment.

INTRODUCTION

Worldwide, there are about 240 million people with HBV infection, with a high rate of infection in China[1]. In the past two decades, hepatitis B transmission has been significantly controlled in China due to the improvement in understanding HBV natural history, strict screening of blood or blood products, the successful development of new antiviral drugs and especially the nationwide implementation of Hepatitis B vaccination. Although the prevention and treatment of hepatitis B infection is still very difficult to achieve, it is no longer impossible to control the spread of hepatitis B.

The epidemiology of Hepatitis B virus in China

According to the World Health Organization, about 2 billion people have been infected with HBV, of which 240 million people are chronically infected. Every year, about 650,000 people die of liver failure, liver cirrhosis and hepatocellular carcinoma (HCC) caused by HBV infection. Globally, the proportion of liver cirrhosis and HCC caused by HBV infection are 30% and 45%[2,3], respectively, while the proportion in China is 60% and 80%[4], respectively. Due to the universal implementation of Hepatitis B vaccination, acute HBV infection has been significantly reduced. Meanwhile, the aging of the infected HBV population, coupled with the widespread use of antiviral drugs cause an elevated proportion of patients with HBeAg-negative CHB[5].

In 2006, the National Hepatitis B serum epidemiological survey showed that the proportion of HBV carriers was 7.18% in the 1 to 59 years old population[6,7]. According to the data, there are about 93 million people with chronic HBV infection, of which 20 million cases are CHB patients. There are areas of high, medium, and low endemicity based on a prevalence of HBsAg positivity of ≥8, 2-7, and <2%, respectively[8,9]. China is a country with a high endemicity, where 90% of new infections occurred among infants and young children due to perinatal or household transmission. As a result of the strict implementation of screening for HBsAg and HBV DNA, transfusions cause rare transmission of HBV. However, there are still other transmissions, such as unprotected sexual contacts, tattoos, and intravenous drug use. Thanks to the introduction of the HBV vaccination and the wide availability of antiviral drugs to treat the primary infection in infected subjects, HBV prevalence has decreased a lot. In 2014, the Chinese Center for Disease Control and Prevention (CDC) conducted a survey on hepatitis B sero-prevalence on 1 to 29 years of age group. The results showed that the prevalence rates of HBsAg positive subjects were 0.32%, 0.94% and 4.38% from 1 to 4, 5 to 14, and 15 to 29 years of age, respectively[10].

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The prevention of Hepatitis B in China

Most of Chinese patients develop chronic infection due to perinatal or household transmission. Efforts to control transmission should, therefore, be focused on preventing infection of newborns. Hepatitis B vaccination is the most effective way to prevent virus transmission. Every newborn in the whole country receives Hepatitis B vaccine[10]. Each pregnant woman who goes to hospital for prenatal care undergoes screening for Hepatitis B. The infants born from HBsAg-positive mothers receive vaccine plus hepatitis B immune globulin (HBIG). With the availability of both hepatitis B immune globulin (HBIG) and hepatitis B vaccine (at first plasma-derived, later recombinant), there was a marked reduction in the infant infection rate. There is still failure occurring in infants born form HBeAg-positive mothers with pre-delivery HBV DNA ≥6 log10 copies/ml[11,12]. Therefore, short-term maternal NAs starting from 28-32 weeks of gestation are advisable for mothers with HBV DNA levels above 6 log10 IU/ml[13,14]. Besides, it was suggested that personnel regarded as high risk, such as medical staff, workers contacting with blood, staff working in child care institution, organ recipient, family members of HBsAg-positive carriers, man having sex with men, should also receive hepatitis B vaccine.

The statement above is crucial to protect those individuals who are at risk. The other important way of prophylaxis is cutting off transmission. It has been concluded that contaminated needles can spread HBV, including intravenous drug users, acupuncture, tattoos, ear piercing and needle prick injuries in hospital settings[15]. Hence, China national medical ministry pays much attention to the disposal of sharp instruments and public health education. Nowadays, disposable needles are used for acupuncture and ear piercing. Besides, education and surveillance concerning the disposal of sharps, the banning of recapping needles, and needle disassembly are also enforced in China.

The management of HBsAg-positive carriers or patients was also emphasized by the government. Those who have been identified as HBsAg positive, should be referred to the Local Disease Prevention and Control Center. The family members of the HBsAg-positive personnel are recommended to check HBV serum markers and those anti-HBs negative members should receive HBV vaccine. Moreover, it was advisable that the HBsAg-positive members are followed up by an infectious disease doctor every 3-6 months[10].

Although great achievements have been reached, China still faces the lack of vaccine programs and use in the undeveloped regions.

THE TREATMENT OF HEPATITIS B IN CHINA

Antiviral therapy

Antiviral therapy is the main strategy for patients with chronic hepatitis B in China, and in the world[16]. The antiviral drugs approved in China are lamivudine, adefovirdipivoxil, entecavir, telbivudine, tenofovir disoproxil fumarate, conventional interferon-alfa (IFN), and pegylated interferona2a (Peg-IFN-2a)[17]. The goal of therapy for chronic HBV infection is to improve the quality of life and survival of the infected person by preventing progression of the disease and prevention of transmission of HBV to others[18]. This goal can be achieved if HBV replication can be suppressed in the majority of people and for a long period. The indications for treatment are generally based mainly on the combination of three criteria: serum HBV DNA levels, serum ALT levels and severity of liver disease (assessed by clinical evaluation, liver biopsy or non-invasive methods). Indications for treatment should also take into account age, health status, family history of HCC or cirrhosis and extra hepatic manifestations. Lamivudine (LAM) is the first drug approved in China in 1999, leading to a decrease of mortality in patients with chronic hepatitis B. At present, the recommended first-line agents include pegylated interferon and 2 nucleotide analogues, entecavir and tenofovir disoproxil fumarate, which have potent HBV-DNA suppression activity and high genetic barrier to resistance. Although prolonged lamivudine (LAM) therapy is associated with the emergence of LAM-resistant mutations, it is still a commonly used therapy in China because of its low cost and long-term safety. Immunomodulatory agents including conventional interferon-a (IFN) and pegylated interferon (Peg-IFN) have been approved in China for more than 10 years[19]. These agents have dual actions: enhancing host immunity to mount a defense against HBV and modest antiviral action. Over the past two decades, IFN-based therapy has been an important treatment for CHB patients. For HBeAg-positive patients receiving Peg-IFN-based treatment, the following baseline predictors are related to a higher sustained response rate, such as HBV DNA $<2\times10^8$ IU / ml, high ALT levels, genotype A or B, low HBsAg levels at baseline, liver inflammation necrosis of G2 or more[20]. However, there are no baseline and on-treatment predictors of response to IFN for the HBeAg-negative petients[21]. The patients who are young (including adolescent patients), or wish to have babies, or want to complete a short-term therapy and those who receive antiretroviral therapy for the first time, may be recommended IFN therapy. Frequent side effects and subcutaneous injection are the main disadvantages of IFN treatment. IFN is contraindicated in patients with decompensated HBV-related cirrhosis or autoimmune disease, in patients with uncontrolled severe depression, and in pregnant women[22].

Limits of current antiviral treatment

The antiretroviral therapy controls the replication of HBV effectively, being shown to decrease hepatic fibrosis or reverse cirrhosis, and to reduce the development of hepatocellular carcinoma (HCC). However, it is difficult to eradicate the virus. HB-

sAg seroclearance, although the ideal endpoint, is only achievable in 10-12% of patients by multicenter trials usually studying relatively young patients[23]. A research showed that it would take 52.2 years to clear serum HBsAg completely, indicating a treatment of decades or even the whole life if choric hepatitis B patients receive current nucleoside (acid) analogues[24]. Moreover, the covalently closed circular DNA (cccDNA) stays in the nucleus of infected hepatocytes persistently, and also, the HBV genome integrates into the host genome and might favor oncogenesis and the development of HCC[25]. So, it is really difficult to achieve sustained off-therapy HBsAg loss.

Due to the high relapse rate after NA treatment discontinuation in patients with chronic hepatitis B, a long-term treatment is generally recommended, which may lead to inevitable drug resistance. Like HIV, the HBV reverse transcriptase lacks a proofreading function, which allows to viral mutations to occur spontaneously during viral replication. Factors that may impact the risk of selecting resistant HBV variants during antiviral therapy include the baseline viral load and diversity, the replicative fitness of variants and the number of specific mutations that are required to confer resistance. The occurrence of drug resistance will not only result in loss of achieved improvement, but also in a rapid deterioration of liver disease, an increase in incidence and mortality of liver transplantation, and primary liver cancer[26]. China pays much attention to resistance to anti-viral drugs. In 2005 China developed the first edition of "Chronic Hepatitis B Prevention and Control Guidelines", promoting the standardization of anti-viral treatment. In 2008, an article about "expert consensus of hepatitis B virus resistance " was published. The concepts related to HBV resistance mutation, detection of drug resistance and other issues, were further standardized. Moreover, the consensus of drug resistance was updated in January 2013[26]. Furthermore, Chinese guidelines on chronic Hepatitis B have been updated in 2015. Current data show that long-term ETV or TDF therapy is relatively safe and has minimal risk of drug resistance. No TDF resistance has been reported up to 7 years[27], which is really exciting news for chronic hepatitis B patients.

FUTURE GOALS

The ultimate goal is eradication of HBV infection by various strategies, including vaccination, treatment and prevention of transmission. There is still a long time for China to control HBV infection completely, although great progress has been made. There are still 93 million people with HBV infection and HBV will continue to prevail in our country for a very long period. Nowadays, there is still some defect in HBV immune strategies; moreover, nucleoside (acid) analogues resistance remains to be solved. The basic characteristics of hepatitis B virus, and the mechanism of infection have been well understood. The knowledge about human HBV infection and its related disease is constantly accumulating. Chinese scientists made a major breakthrough in HBV receptor research. In 2012, the team of Prof. Li Wenhui from Peking Institute of Life Sciences found that sodium taurocholate cotransporting polypeptide was a functional receptor for human hepatitis B and D virus[28]. This finding not only can help us to further understand the HBV life cycle, but also highlights the importance for new antiviral approaches. At the same time, China has implemented a positive hepatitis B immune strategy, including vaccination for the newborn and adolescent less than 15 years of age that did not receive effective vaccination at birth. New hepatitis B infection has markedly decreased due to the immune strategy. With Guidelines for The Prevention and Treatment of Chronic Hepatitis B and the standardization of antiviral therapy, chronic hepatitis B-related mortality has decreased, leading to control of HBV prevalence and great contribution to public health of China.

Further research on hepatitis B pathogenesis is currently ongoing in China and the results could actively contribute to the global fight against the disease.

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