

Recollection

Control of Chronic Hepatitis B in China: Perspective of Diagnosis and Treatment

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In the last three decades, China has made extraordinary effort and achieved great progress in the control of hepatitis B. Thanks to the adoption of universal administering of HBV vaccinations for newborns since 1992, the prevalence of hepatitis B surface antigen (HBsAg) in the population born after 1992 decreased significantly resulting in a decline in the general population from 9.75% to about 6% (1). In the last 10 years, under the support of national major scientific research grants, many multicenter, randomized controlled trials (RCTs) have been conducted, generating more and more clinical evidence for antiviral therapy for chronic hepatitis B (CHB) (2). From 2005 to 2019, 4 editions of “Guidelines on the Prevention and Treatment of Chronic Hepatitis B” were jointly issued by 2 sister branches of the Chinese Medical Association including the Chinese Society of Hepatology and Chinese Society of Infectious Diseases (3–6). Sustained effort on continued medical education based in the clinical guidelines have raised the knowledge base of specialists and internists and improved the standard of care for CHB (7). Recently, the National Healthcare Security Administration has conducted government negotiations to massively reduce the price of antiviral medicine. The improvement of the reimbursement policy together with increased patient accessibility and affordability for antiviral therapy have increased the uptake of antiviral therapy and improved the clinical outcomes (8). As a result, considerable progress has been made in diagnosis and treatment, making it possible to control hepatitis B in China.

IMPROVEMENTS IN DIAGNOSTIC MODALITY

In recent years, new serological markers, transient elastography (TE), and novel pathological criteria in the diagnosis of CHB have been extensively investigated and increasingly used in China. Conventional HBV serological markers have been widely used in patients with CHB to establish the phases of HBV infection

and guide antiviral therapy. Recently, the clinical utility of some novel markers have been investigated in patients with HBV infection. Quantitative HBsAg (qHBsAg) levels are correlated with intra-hepatic covalently closed circular DNA (cccDNA) and can predict treatment response (9). Baseline anti-HBc quantification (qAnti-HBc) may serve as a useful marker indicating ongoing host-immune activity against HBV, with high levels of anti-HBc being used to predict the loss of hepatitis B envelope antigen (HBeAg) (10–12), the efficacy of antiviral therapy (13–14), and the absence of HBV relapse after treatment cessation (15). HBV core-related antigen (HBcrAg) is a novel serum marker measuring composite viral protein and considered to be a surrogate marker of intrahepatic HBV cccDNA. A decrease in HBcrAg is related to the loss of HBeAg and HBsAg and the safe discontinuation of antiviral treatment. HBcrAg may also be helpful for predicting hepatocellular carcinoma (HCC) development. Serum pre-genomic RNA (pgRNA) transcribed from HBV cccDNA has a strong correlation with intrahepatic cccDNA and is considered to be an indirect marker of reservoir size (16–17). These novel serum markers provide useful tools for better monitoring of disease progression and evaluation of the efficacy of antiviral therapy.

TE is a noninvasive tool with ease of operation, good repeatability, and reasonable accuracy for identifying liver fibrosis or early cirrhosis. A multicenter study validated the diagnostic performance of TE measured by FibroScan to stage liver fibrosis in a cohort of 469 Chinese patients with CHB (18). Another device for TE measurement (FibroTouch) has also confirmed its clinical utility in a single-center prospective study including 435 chronic liver disease patients including 237 CHB patients (19).

To quantitatively measure the degree of liver fibrosis in CHB patients, an automatic digital technique qFibrosis has been investigated and shown promising results (20). In complementary to Ishak modified histology activity index (HAI) and Ishak fibrosis score, a new classification (Beijing Classification) has been

proposed by Chinese investigators that further divides fibrosis beyond stage 3 into predominantly progressive, indeterminate, and predominately regressive (P-I-R score) to assess the dynamic changes in fibrosis pre- and post-antiviral therapy (21). Recently, one study using the Beijing classification found that liver fibrosis progression was associated with low serum HBV DNA level (20–200 IU/mL) at week 78 of nucleoside (nucleotide) analogue (NA) therapy, indicating that switching to or adding a more potent antiviral agent would benefit these patients (22).

IMPROVEMENT IN CLINICAL STUDIES OF ANTIVIRAL THERAPY

In the last decade, both the number and quality of clinical studies on treatment of HBV has dramatically improved (2). A large number of studies conducted by Chinese hepatologists showed that NA treatment can strongly suppress virus replication, improve liver histology, reduce the risk of complications and HCC progression, and reduce liver related all-cause mortality (23–27). An observational study showed that entecavir (ETV) monotherapy is associated with less virological breakthroughs and potentially higher HBV-DNA suppression than de novo combination of lamivudine (LAM) and adefovirdipivoxil (ADV) during 3 years of treatment for naïve HBV-related compensated liver cirrhosis (28). Another real world study also demonstrated that ETV was efficacious and well tolerated through 48 weeks of treatment in a heterogeneous Chinese CHB population (29). A nationwide observational study showed that more than 50% of patients with CHB in Tier-2 city hospitals in China initially received ETV therapy, which not surprisingly was more effective than LAM-based treatments and associated with lower rate of treatment modification (30).

Effective viral suppression is necessary to reduce HCC development in cirrhotic patients (31). Tenofovir disoproxil fumarate (TDF) and ETV are first-line therapies, and in recent years, controversy exists on which one is superior to reduce the risk of HCC development. A meta-analysis was performed by Chinese researchers to clarify this issue with critical clinical and methodological considerations, showing that disparities in follow-up duration may be a key factor to influence the results (32).

Combination or sequential strategies based on the potent antiviral effect of NA and immune modulation of interferons (IFN) have been extensively explored in China. Based on evidence from the “Optimising

HBeAg Seroconversion in HBeAg-positive CHB Patients with Combination and Sequential Treatment of PegIFN alfa-2a and ETV” (OSST) study, “Switching to PegIFN a-2a in NUC treated CHB patients ” (NEW SWITCH) study, Endeavor Study, and Anchor study, Chinese researchers proposed a roadmap for NA-Peg-IFN sequential therapy. In particular, in patients who achieved undetectable HBV, the loss of HBeAg, and a low level of HBsAg (<1,500 IU/mL) under NA therapy, adding or switching to Peg-IFN could yield a relatively higher rate of HBsAg loss ((and a low level of HBsAg (<1,500 IU/mL) under NA therapy, adding or switching to Peg-IFN could yield a relatively higher rate of HBsAg loss (33–39). Furthermore, a prospective cohort study from China showed that Peg-IFN α -2a-based therapy could reach high rates of HBsAg clearance (29.8% and 44.7% at week 48 and 96, respectively) and seroconversion (20.2% and 38.3% at week 48 and 96, respectively) in patients diagnosed as inactive HBsAg carrier status (40).

UPDATE OF GUIDELINES AND OF EDUCATION ACTIVITY

The guidelines on the Prevention and Treatment for Chronic Hepatitis B were first jointly published by the Chinese Society of Hepatology and Chinese Society of Infectious Diseases in 2005, and updated in 2010, 2015, and 2019. The 2019 version of the guidelines has two important changes (3). First, antiviral therapy is recommended if aminotransferase (ALT) is higher than 1 times instead of 2 times of the upper limit of normal levels (ULN, 40 IU/L for both men and women) for those with evidence of cirrhosis, intermediate degree of necroinflammation/fibrosis on non-invasive modality or on liver histology, older than 30 years, or family history of HCC/cirrhosis. This expansion of treatment indications will convey the benefit to antiviral therapy for larger populations, thereby reducing the risk of disease progression. Secondly, ETV, TDF, tenofovirafenamide (TAF), and Peg-IFN α are recommended as the first-line choice for treatment of naïve patients, which is in line with recommendations from the World Health Organization (WHO), American Association for the Study of Liver Diseases (AASLD), Asian Pacific Association for the Study of the Liver (APASL) and European Association for the Study of the Liver (EASL); however, LAM, telbivudine (LdT), and ADV are not recommended.

With the update of the guidelines, educational activities, and training programs were conducted to improve the standard of care (SOC) for CHB in China, especially in health resource limited areas. A 3-year initiative titled “China Grassroots Hepatitis B Prevention & Treatment Training Program” was implemented by the Chinese Society of Hepatology and Chinese Society of Infectious Diseases from 2015 to 2017. Totally, 58 training sessions of 1-day courses covered nearly 10,000 primary care physicians from 31 provincial-level administrative divisions (PLADs). In 2018, the China Health Promotion Foundation launched the another 3-year hepatitis training program: “Poverty Alleviation and Health Preservation-Hepatitis Prevention and Treatment”. In this program, the hepatologists and infectious disease doctors went to the remote and small cities in the 12 PLADs of western China to give the public education and clinical training to local doctors. In parallel, over 300 local physicians from the western part of China came to the 8 designated centers of excellence in Beijing, Shanghai, Guangzhou, and Chengdu for 3-months of onsite clinical training.

REIMBURSEMENT POLICY AND MASSIVE PRICE REDUCTIONS FOR ANTIVIRALS

With economic and social development, the pricing and reimbursement policies have been steadily improved. Data from Beijing indicated that coverage of antiviral therapy by basic medical insurance since 2011 has reduced the risk of developing liver-related death for patients with CHB (8). The selection of a potent NA with high barrier to resistance as a first-line therapy, especially in areas with limited healthcare resources, may provide the best chance of achieving treatment goals (41). Until 3 years earlier, NA with high barrier to resistance like ETV and TDF had been much more expensive, so they were not widely used. To make a change, the government sectors, medical community, civil societies, and manufacturers have made joint efforts. Through government negotiation, the prices of TDF and TAF have reduced by >50% and have been included in the basic medical insurance in the mainland of China. In 2019, the price of generic ETV and TDF has reduced to less than 10 yuan RMB per month in 11 PLADs. Indeed, data from the China Registry of Hepatitis B (CR-HepB) showed that among all CHB patients who received NA therapy, the proportion of those who received ETV and TDF had

increased from 13.5% in 2003 to 79.7% in 2016 (42), and the proportions in cirrhotic patients increased from 41.9% in 2010 to 92.8% in 2019 (43).

PERSPECTIVE ON THE MASSIVE TEST-AND-TREAT STRATEGY

Although the number of people with new HBV infections will become smaller, there are still an estimated 80 million people that are positive for HBsAg (44). According to the POLARIS modeling study, in the mainland of China, only around 20% of those chronically infected with HBV were actually diagnosed and 10% of those who were eligible to be treated received treatment (45). Investment case modeling studies suggested that if we only treat the few millions of CHB who are already on the treatment, the HBV-related cirrhosis/HCC mortality will still be increasing over the next two decades; on the other hand, if we scale up test-and-treatment strategies and treat most or even all persons who need the treatment, the HBV-associated mortality will dramatically decline, which is cost-effective or even cost-saving (46). For example, if the treatment coverage increased from current practice (12.5%) to 100% from 2018, the numbers of chronic HBV infections, new HBV infections, and HBV-related deaths in 2035 would be reduced by 26.60%, 24.88%, and 26.55%, respectively, and in 2050, it would be reduced by 44.93%, 43.29%, and 43.67%, respectively (47). Therefore, we can conclude that implementations of HBV vaccination and increasing the test-and-treat coverage strategies are the most important and effective in controlling CHB in China.

SUMMARY

There is no doubt that China has made great achievements in the prevention and treatment of CHB. Predictably, in the future, the prevalence of HBsAg in the general population and HBV-related morbidity and mortality will further decline if we continue the current prevention measures and adopt massive test-and-treat strategies. Finally, development of novel therapies aiming to clear HBsAg is under way. Therefore, we are confident that China will succeed in achieving the goal of eliminating hepatitis as a public health threat by 2030.

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