

Chronic hepatitis B virus infection: epidemiology, prevention, and treatment in China

Rui Yu, Rong Fan, Jinlin Hou (✉)

Hepatology Unit and Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China

© Higher Education Press and Springer-Verlag Berlin Heidelberg 2014

Abstract Chronic hepatitis B is a major health problem in China. The universal vaccination program since 1992 has changed the epidemiology of hepatitis B virus infection in China from highly to moderately endemic. The most prevalent hepatitis B virus strains in China are genotypes B and C, whereas those in western provinces are genotypes D and C/D hybrid. Chronic hepatitis B poses a heavy burden to the society in China. Different treatment strategies have been explored to improve patient outcomes in a cost-effective manner. However, antiviral drugs with a low genetic barrier to resistance are still extensively used because of the generally low income and limited resources in China. Individualized antiviral therapy is closely associated with translational medicine, which utilizes information from studies on genomics, immune biomarkers, and fibrosis. The results of these studies are crucial in further improving treatment outcomes.

Keywords chronic hepatitis B; epidemiology; prevention; treatment

Introduction

Hepatitis B virus (HBV) is a major global pathogen. More than 240 million people have chronic liver infections, and approximately 600 000 people die every year because of the acute or chronic consequences of hepatitis B [1]. The long-term hepatic effect of HBV infection varies from minimal hepatic inflammation to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC), leading to high morbidity and mortality [2]. In China, chronic hepatitis B (CHB) infection as the leading cause of HCC [3] poses a heavy burden to the society and patients. Remarkable progress in disease management has been achieved with the implementation of universal infant immunization since 1992 and with the development of antiviral drugs in the past decade. The increasing demands for optimal treatment outcomes in specific individuals have placed utmost urgency on the development of translational medicine-based individualized therapy. This review summarizes the recent progress in the epidemiology, prevention, treatment options, and challenges for CHB in China.

Epidemiology and prevention of chronic hepatitis B

Vaccination program and prevalence changes

The national hepatitis sero-epidemiological survey in 1992 revealed that the prevalence of hepatitis B surface antigen (HBsAg) in individuals aged 1 to 59 years was 9.75% in China. This finding classified the mainland of China as a high-HBV-prevalence region. However, hepatitis B is preventable by immunization. Perinatal or early childhood transmission is the mainly cause of CHB in China. Therefore, universal hepatitis B vaccination is the best, cost-effective preventive strategy for hepatitis B control. Since 1992, the Ministry of Health has implemented a series of regulation policies on the management of hepatitis B vaccination. The routine three-dose active HBV immunization was recommended to all infants in 1992; in 2002, the government obliged all local authorities to provide free HBV vaccination to all infants and only required service fee for the vaccination procedure. Nevertheless, immunization coverage remains relatively low in rural areas and in the western part of China because of the uneven economic conditions across the country. The government implemented a completely free HBV vaccination program for all neonates in May 2005. The

second national survey of HBV sero-epidemiology showed a decrease (to 7.18%) in the general prevalence rate of HBsAg in 2006 and a decrease (from 9.67% to 0.96%) in the prevalence rate of HBsAg in children below 5 years of age. This great achievement has changed the epidemiology of HBV infection in China from highly to moderately endemic [4]. However, the prevalence of HBsAg can be further decreased by maintaining free immunization of infants and targeting timely birth dose to reach all newborns in the coming years across China. In addition, expanded vaccination is necessary to prevent HBV infection in adolescents and adults who have missed the newborn vaccination or who are at high risk of HBV infection.

Geographical distribution of HBV genotypes

The most prevalent HBV strains in western countries are genotypes A and D, whereas those in China are genotypes B and C, which possibly lead to different levels of disease progression [5]. A total of 1096 chronic HBV carriers were analyzed from nine provinces in the mainland of China, with genotypes A, B, C, and D having prevalence rates of 1%, 41%, 53%, and 4%, respectively. Genotypes E, F, G, and H were not detected in China. In addition, a north-south division in the distribution of genotypes B and C exists. Genotype C is predominant in Northern China (77%), whereas genotype B is predominant in southern provinces (59%). Genotype D is principally found in Northwestern China [6]. In Tibet Autonomous Region and Gansu Province, two C/D hybrid patterns were first identified [7]. The presence of these hybrid patterns increased the genetic diversity of HBV. Different ethnic groups of five provinces were further studied; the HBV C/D recombinant is restricted to the Qinghai-Tibet Plateau in Western China and predominantly in Tibet where family-cluster HBV infection is common [8,9].

Heavy burdens and critical challenges in a resource-constrained area

The long-term and recurring effects of HBV infection are compounded by the frequency of delayed consultation. Patients with CHB need long-term treatment, which incurs a high cost for patients with advanced liver disease. Therefore, CHB poses a considerable economic burden on the Chinese healthcare system, the patients, and their families. Sustained suppression of serum HBV DNA to low or undetectable levels by antivirals helps prevent liver disease progression and minimize HCC risks [10]. Proper treatment is critical for preventing downstream liver disease, reducing mortality, and improving the quality of life. However, the generally low income in China has been the main barrier in providing proper treatment. In the past, most patients pay their own treatments for limited reimbursement. The Chinese healthcare system has recently shown some amended

policies. Conventional and pegylated interferons (PEG-IFN) and nucleos(t)ide analogs (NAs) have been included into the new national reimbursement list, and the health insurance has covered the majority of patients in rural and urban areas. However, the reimbursement is still limited. The government funding to public providers still cannot sufficiently cover the direct and indirect disease costs. Therefore, most naïve CHB patients cannot initiate treatment following major international recommendations to use potent antiviral agents. The data of the China Registry of Hepatitis B (CR-HepB) showed that drugs with low antiviral potency or low genetic barrier are still widely used in China (Fig. 1). These drugs include lamivudine (LAM), adefovir (ADV), and other drugs without certain antiviral efficacy. The long-term use of these drugs increases the rate of resistance or poor response.

Treatment strategy

The existing problems in China have placed urgency in the development and assessment of treatment strategies based on specific national conditions. The Chinese Society of Hepatology and the Chinese Society of Infectious Disease published a new evidence-based guideline in 2010 for the management of CHB in China. The currently available antiviral agents for CHB treatment in China include standard IFN α (2a, 2b, 1b); PEG-IFN α (2a, 2b); and all five NAs, namely, the L-nucleoside analogs LAM and telbivudine (LDT), the deoxyguanosine analog entecavir (ETV), and the acyclic nucleoside phosphonates ADV and tenofovir disoproxil fumarate (TDF). TDF was only approved for HIV treatment in China until October 2013. These drugs have different long-term efficiency rates because of their particular potency and drug resistance patterns (Table 1). ETV, TDF, and PEG-IFN were recommended as first-line drugs in major international guidelines [11–13]. In the Chinese guideline, all NAs are recommended as first-line therapy, although high-potent and low-resistance agents are preferred. This compromise is mainly due to the highly heterogeneous economic situations across China, where ETV or TDF may not be reimbursable, not affordable, or not available. IFNs could be chosen for patients without decompensated liver cirrhosis who require finite duration because of their non-resistance and relatively high HBeAg and HBsAg seroconversion rates.

IFN- α based therapy and early stopping role

IFN- α has been used against HBV for over 30 years and has been approved without limitations in its pegylated form. IFN- α and PEG-IFN have dual actions: enhancing host immune system to defend against HBV and modest antiviral action. PEG-IFN has well-known advantages and disadvantages. On the one hand, PEG-IFN achieves an approximately 30% hepatitis B e antigen (HBeAg) seroconversion rate after a finite standard of care for 48 weeks. On the other hand, it is

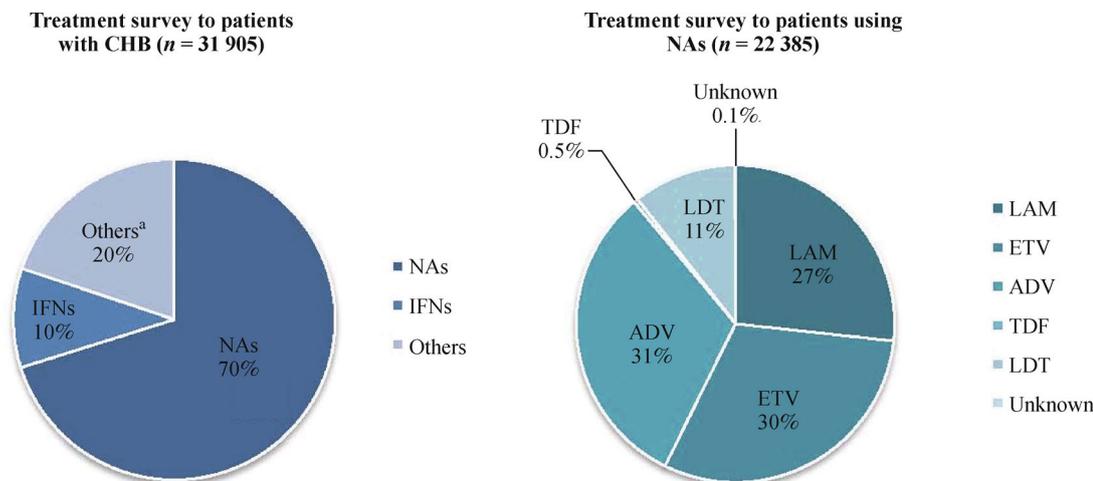


Fig. 1 Distribution of antiviral drugs for chronic hepatitis B used in clinical practice in China. June 2012 to December 2013 (Data from 31 905 patients enrolled in treatment survey in China Registry of Hepatitis B). CHB, chronic hepatitis B; NAs, nucleos(t)ide analogs. IFNs, interferons; LAM, lamivudine; ETV, entecavir; ADV, adefovir; TDF, tenofovir; LDT, telbivudine. ^a including hepatic protectant, immunomodulator, traditional Chinese medicine and drugs unknown.

burdened with significant side effects and contraindications. Particularly, it should be used with major caution in patients with cirrhosis owing to its risk of potentially fatal hepatic failure. In addition, treatment with PEG-IFN should be limited to patients with a favorable baseline profile and to those who achieve early response. For instance, Janssen *et al.* identified genotype-specified stopping rules in HBeAg-positive CHB patients treated with PEG-IFN. For patients with genotypes A or D, no decline in HBsAg at week 12 predicts low response rates (negative predictive value: 97% to 100%); for patients with genotypes B or C, HBsAg > 20 000 IU/ml at week 12 is associated with a low probability of subsequent HBeAg seroconversion (negative predictive value: 92% to 98%) [14]. For all patients irrespective of HBV genotype, HBsAg level > 20 000 IU/ml at week 24 may be used as a stopping rule (Fig. 2). Prolonged treatment or addition of NAs are always preferred for patients without early responses. However, this theoretical strategy has yet to be determined in a well-designed clinical trial. In China, the EXCEL study (NCT00734162) [15] was conducted to explore whether or not response-guided therapy can be used to optimize PEG-IFN α -2a treatment. In this study, 264 patients with HBeAg-positive CHB were enrolled to receive PEG-IFN α -2a treatment for 24 weeks. Early responders (defined as HBsAg < 1500 IU/ml and HBV DNA < 10⁵ copies/ml at week 24) received PEG-IFN α -2a for another 24 weeks. Non-early responders were randomized to receive PEG-IFN α -2a for another 24 weeks, prolonged treatment of PEG-IFN α -2a for another 72 weeks, or addition of ADV. Mean decline in quantitative HBsAg from baseline to 24 weeks after the treatment was higher in early responders than in non-early responders (-1.15, -0.67, -0.71, and -0.64 log₁₀ IU/ml, respectively), and the HBsAg loss rates were

4.5% (3/66), 0% (0/67), 1.5% (1/67), and 3.1% (2/64), respectively. No significant difference was observed among groups of non-early responders in any other efficacy endpoints. The results demonstrated that the early responders to PEG-IFN α -2a had a high rate of HBsAg loss. However, prolonged duration or addition of ADV may have no effect on the treatment efficacy for non-early responders. Therefore, new strategies must be discovered to further improve the efficacy for this subpopulation. In patients with HBeAg-negative CHB, baseline predictors of response to PEG-IFN are poorly defined compared with HBeAg-positive disease. Janssen *et al.* [16] conducted a multicenter, randomized, double-blind, controlled trial to explore whether or not early on-treatment predictors of sustained response enable on-treatment adjustment in patients with HBeAg-negative CHB treated with PEG-IFN. They found a combination of decline in serum HBV DNA (< 2 log₁₀ copies/ml) and absence of HBsAg level decline from the baseline at week 12 can be established as a stopping rule, in which therapy could be discontinued without a loss of sustained responders.

HBsAg loss is rare among NAs-treated patients who maintain HBV DNA suppression. The OSST study (NCT00940485) [17] was conducted to compare the efficacy by switching to PEG-IFN α -2a or continuing ETV treatment in 200 patients who responded to ETV (HBV DNA < 300 copies/ml and HBeAg < 100 PEIU/ml). The on-treatment reductions in HBsAg and HBeAg were significantly greater with PEG-IFN α -2a than with ETV. A large proportion of the patients who switched to PEG-IFN α -2a achieved HBeAg seroconversion at week 48 compared with continued ETV (15.5% vs. 6.0%). Only patients in the PEG-IFN α -2a arm achieved HBsAg loss (9.3%). This result indicates that CHB patients may discontinue long-term NAs therapy by switch-

Table 1 Latest results of major clinical studies on the efficacy and drug-resistance of nucleos(t)ide analogs

Nucleos(t)ide analogs	Lamivudine		Adefovir		Telbivudine		Entecavir		Tenofovir	
	N	P	N	P	N	P	N	P	N	P
HBeAg status	N	P	N	P	N	P	N	P	N	P
Duration (year)	3	5	5	5	4 ^b	4 ^b	3	5	7	7
HBV DNA <300–400 copies/ml (%)	40	NA	53	39	86.4	76.2	98	94	99	99
HBeAg seroconversion (%)	/	44 ^a	/	30	/	53.2	/	23	/	40
HBsAg loss (%)	NA	NA	5	2	0.6	1.9	NA	1.4	NA	12
HBV resistance (%)	NA	71	29	20	15.9	18.8	1.2 ^c	0	0	0

N, negative; P, positive; NA, not available.

^aCumulative.

^bExcluding those with resistance on year 2.

^cData for 6 years.

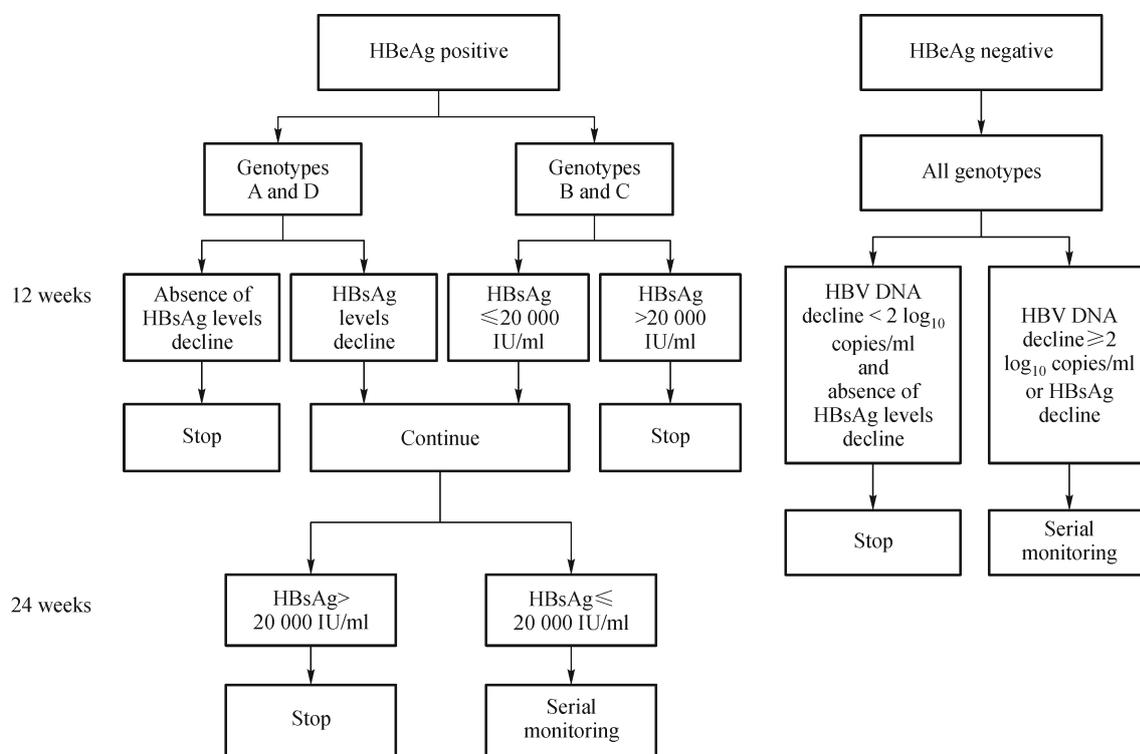


Fig. 2 Response-guided therapy for pegylated interferon treatment in patients with chronic hepatitis B.

ing to a finite course of PEG-IFN α -2a. A response-guided approach of sequential antiviral therapy may identify patients with a high possibility of success. However, the treatment strategy has several limitations. Viral rebound as a reduction of efficacy occurred in 39 patients when switched to PEG-IFN α -2a. Post-treatment data for further follow-up are still needed to assess the durability of the response.

Overall, patients should be carefully selected for initial IFNs therapy or extended therapy by using predictors at baseline or according to the on-treatment response. Further studies are needed to clarify the individualized tailoring of PEG-IFN treatment [18].

NAs-based therapy

NAs, which inhibit the reverse transcription of hepatitis B polymerase, are an important class of drugs that changed the treatment paradigm and prognosis of CHB. Oral NAs therapy has advantages over IFN therapy because of its potent antiviral effects, good tolerance, minimal side effects, and convenience. The major shortcomings of this therapy are drug resistance, low HBsAg loss rate, and high virological relapse rate when treatment is discontinued or interrupted because of low adherence, necessitating long, and indefinite treatment.

Initial monotherapy

In international guidelines [11–13], potent HBV inhibitors, such as ETV and TDF, are recommended as first-line monotherapies. Both drugs achieved high rates of HBV DNA suppression and ALT normalization, which were associated with low rates of resistance development in NAs-naïve patients during long-term therapy. Long-term treatment of ETV shows good efficacy and a low resistance rate of only 1.2% after 6 years [19,20]. TDF monotherapy is effective in suppressing HBV DNA through 7 years with no evidence of TDF resistance [21]. In addition, the long-term suppression of HBV with TDF benefits the regression of advanced liver fibrosis and cirrhosis [22]. However, for financial and social reasons, the other three drugs are also listed as first-line therapy in the 2010 version of the Chinese guideline. LAM and ADV are inexpensive agents; however, both engender high rates of resistance with long-term monotherapy [23]. ADV is less efficacious, engendering high rates of resistance [24]. Patients with an HBV DNA level of more than $3 \log_{10}$ copies/ml at 6 months of LAM therapy have a 63.2% chance of developing YMDD variants within 29 months of follow-up [25]. However, LAM may remain an effective first-line therapy for HBeAg-positive patients with baseline HBV DNA $< 6.6 \log_{10}$ copies/ml [26]. LDT is a potent inhibitor of HBV replication; patients with high baseline HBV DNA levels and detectable HBV DNA after 24 weeks of therapy have a high incidence of resistance [27]. However, patients with low baseline HBV DNA combined with negative HBV DNA at week 24 obtain good therapeutic results with LDT [28]. Thus, selecting patients who may respond well without developing virological breakthrough is crucial.

Initial combination therapy

Combination therapy is the current standard of care for the treatment of human immunodeficiency virus infection. It is superior to sequential monotherapy in terms of efficacy and prevention of drug resistance. In the treatment of CHB with first-generation NAs, ADV and LAM, two controlled trials compared the efficacy and safety between combination therapy and monotherapy. These studies revealed minimal additive or synergistic antiviral effects of combination therapy over monotherapy; in addition, the decline in HBV DNA levels and HBeAg and HBsAg seroconversion rates was comparable between groups [29,30]. Among the approved NAs, ETV and TDF have potent antiviral activities with a non-overlapping pattern of resistance. Lok *et al.* [31] conducted a randomized, open-label, multicenter, phase IIIb superiority study to compare the efficacy and safety of ETV monotherapy with those of a combination of ETV and TDF. They found that the antiviral efficacy of ETV monotherapy is similar to that of ETV plus TDF combination therapy over 96 weeks of treatment. Thus, combination therapy cannot be

recommended as first-line therapy for typical patients with CHB because of insufficient evidence regarding its efficiency [32].

Response-guided therapy

Starting treatment with high barrier to resistance is crucial to minimize the development of resistance, preserve future treatment options, and maximize the chances of long-term treatment success. However, the high daily costs of ETV and TDF limit their widespread use in China. Drugs (LAM, ADV, or LDT) with low cost and low genetic barrier to resistance are still used extensively. To better manage antiviral treatments that use drugs with low genetic barrier in the Asia-Pacific region, a panel of hepatologists proposed the “Roadmap concept” in 2007 [33]. This strategy suggests that patients with suboptimal response after 24 weeks of initial drug treatment switch to a potent agent or add a second agent without cross-resistance. However, this proposal is based on expert opinion and retrospective analysis. Therefore, Sun *et al.* [34] conducted the Efficacy Optimization of Response to Telbivudine (EFFORT) study (NCT00962533) to prospectively evaluate the efficacy and safety of the Roadmap strategy by adding ADV to LDT for suboptimal responders. A total of 606 HBeAg-positive CHB patients were enrolled in the study. The final two-year results showed that, compared to the Mono group, more patients in the Optimized group achieved HBV DNA < 300 copies/ml (76.7% vs. 61.2%, $P < 0.001$) with less genotypic resistance (2.7% vs. 25.8%, $P < 0.001$) at week 104. For week 24 suboptimal responders, LDT plus ADV showed an additive antiviral potency, with 71.1% achieving virological response at week 104 and only 0.5% developing genotypic resistance, compared with 46.6% who achieved virological response and 37.8% who developed genotypic resistance with LDT monotherapy. Thus, optimization strategy successfully proved the benefits by adding ADV to patients of suboptimal virological responses with additive antiviral potency and low resistance. However, the long-term resistance rate of the optimization strategy is still needed to be investigated in the extension study. In addition, as around two-thirds of patients in the Optimized group were treated with combination therapy, cost effectiveness is another concern.

Rescue of patients with drug resistance

Despite the recent development in antiviral drugs, drug resistance has been a serious challenge in China because of the widespread use of drugs with low genetic barrier. Therefore, mandatory monitoring is necessary in case of viral resistance and breakthrough. In patients with LAM-resistant HBV infection, switching to or adding on an approach has been controversial for a long time, and no differences in the rates of response or virological breakthrough were evident after 12 months of treatment [35].

Combination therapy has shown superiority over ADV monotherapy in preventing ADV resistance after long-term treatment [36,37]. Despite the good efficacy of ADV in controlling HBV replication, a degree of cross-resistance still exists [38,39]. Thus, the combination of ADV and LAM is proven superior to ADV alone in preventing the subsequent development of multidrug-resistant HBV. In addition, with respect to the non-resistance and finite course of PEG-IFN α -2a-based therapy, a randomized control trial was conducted to compare the efficacy of PEG-IFN α -2a and ADV treatment for CHB patients with LAM resistance [40]. Although the HBeAg seroconversion rate at week 72 after 48 weeks of PEG-IFN α -2a treatment was higher than continuous ADV therapy (25.5% vs. 7.7%), the viral suppression rate (defined as HBV DNA < 80 IU/ml) was suboptimal in both treatment arms at week 72 (10.6% vs. 22.5%). Thus, the efficacy of PEG-IFN α -2a in the rescue treatment of patients with LAM resistance is not as optimistic as expected. For patients with CHB with ADV-resistant, ETV-resistant, or TDF-resistant HBV mutations, few comparison studies of NAs therapy was conducted, as resistance to these agents is less or the time for these drugs being available are shorter. Nonetheless, the LAM-resistance studies support the use of combination therapy in patients with drug-resistant HBV. With the availability of new and potent NAs, particularly ETV and TDF, studies have recommended switching to high potent drugs without cross resistance [41,42]. However, the efficacy of switching to an agent with cross resistance is not optimistic and thus should be avoided. Among the LAM-resistant patients who switched to ETV, 15% developed ETV resistance after 96 weeks of treatment [43]. The rescue therapy of multidrug-resistant CHB with the combination of ETV and TDF showed high efficacy and safety in a specific subset of difficult-to-treat patients with resistant HBV strains, leading to rapid HBV DNA suppression and avoidance of unnecessary changes [44].

Compliance of patients

Although medications and therapies are effective in suppressing HBV infection, the virus cannot be eradicated in infected hepatocytes. Thus, long-term antiviral therapy is needed in the majority of patients. During the long-term treatment period, the adherence among patients who receive NAs is important for management of CHB. Lok *et al.* [45] analyzed the persistence rates and the adherence rates to NAs therapy based on the data of 11 100 patients with CHB. The results showed that the one-year persistence rate is 81% in this study, which is higher than those of hypertensive medications and statins. One possibility may be that the patients perceived that hepatitis B is a serious illness than hypertension or hypercholesterolemia. However, younger and newly diagnosed patients had a low adherence rate. It is probably that young patients are generally less concerned about their health

than old patients; moreover, these patients mostly consider themselves invincible. The low adherence among new patients might be due to the inadequate understanding of their illness or insufficient reinforcement of medication adherence by physicians. In China, detailed patient education always cannot be guaranteed because of the relatively limited medical resources. Therefore, specialty practices should be provided for hepatitis B in China for better patient education and counseling on medication adherence.

Future perspective

Despite many treatment strategies being applied, the treatment results are still far from satisfactory. Thus, individualized therapy of CHB was proposed to explore different treatment strategies based on the characteristics of individual patients. In China, the focus of research is on exploring HBV-related biomarkers from studies on genomics, virology, immunology, and fibrosis to further improve the efficacy of antiviral therapy.

Genome wide association study (GWAS)

GWAS is an examination of many common genetic variants in different individuals to detect any associations between single nucleotide polymorphisms and diseases. In the genetic study of HBV infection, susceptibility to virus and HBV-related HCC has been extensively researched. By contrast, little is known about the association between treatment responses and genome polymorphism. Most recently, 1161 Chinese patients were included from optimization-based clinical trials to explore relationships between treatment responses and genome polymorphism. All blood samples were scanned by Human OmniExpress Exome chip, which can detect a variation of more than 70 million in each sample while adding more than 200 000 custom exon mutation sites, thereby ensuring the high quality of data and content. Currently, 1145 effective results (average call rate > 99.9%) were obtained. Patients with different response gene polymorphisms were found with different treatment responses after initial analysis, suggesting the important implications for patients to optimize or adjust treatment strategy. Refined analysis and validation studies are ongoing to further investigate the mechanism.

High-throughput DNA sequencing

Quasispecies arise from rapid genomic evolution powered by the high mutation rate of RNA viral replication [46]. The application of quasispecies theory to HBV populations has boosted our understanding of interactions within mutant spectra. Cloning and subsequent Sanger dideoxy sequencing have been widely used in the analysis of HBV quasispecies heterogeneity [47]. However, this procedure is time consum-

ing and costly, and only limited clones were obtained within a patient sample. Ultra-deep sequencing technologies have changed the situation dramatically. They allow for massively parallel picoliter-scale amplification and detection of individual DNA molecules. Hundreds and thousands of clones can be obtained within a single sample. We obtained response-guided samples from an HBV patient cohort who underwent therapy by using the ultra-deep sequencing technology for in-depth microevolution analysis of the evolving dynamics of their quasispecies pools detected by ultra-deep sequencing. The genetic analysis revealed that the virological responses of patients to chemotherapy are determined by the composition of the critical drug-resistant mutants at the early stage of treatment. The detailed genetic mechanism allows us to propose a conceptual roadmap for future studies of antiviral therapy.

Immune biomarkers

The treatment goal of anti-HBV therapy is to reconstruct HBV-specific immune function and achieve the seroconversion of HBeAg and HBsAg. The exploration of host-based predictors of efficient and immunologic strategies is indispensable because of the important functions of the host immune system in the antiviral process. Ma *et al.* [48] proposed that the serum concentration of interleukin-21 (IL-21), a newly discovered cytokine with wide and efficient immune functions, can be used as an independent predictor of HBeAg seroconversion for patients who received LDT treatment for 12 weeks. Li *et al.* [49] found that circulating chemokine (C-XC motif) receptor 5 (CXCR5)⁺CD4⁺ T cells have important functions in facilitating HBeAg seroconversion in patients with chronic HBV infection by producing IL-21. These results indicate that IL-21 is a plausible biomarker that might contribute to the individualization of antiviral therapy for HBeAg-positive CHB or to the development of immunotherapies for CHB.

Assessment of liver fibrosis

Alanine aminotransferase (ALT) > 2 times the upper limit of laboratory normal was taken as the indicator of significant hepatitis among non-cirrhotic patients who may warrant antiviral therapy. However, recent data have increasingly recognized that patients with normal or mildly elevated serum ALT are not guaranteed to be free from liver damage. Antiviral therapy should be recommended if significant hepatic necroinflammation or fibrosis is detected on liver biopsy irrespective of the ALT levels. Thus, assessment of liver fibrosis is important in selecting patients for treatment. Liver biopsy is the gold standard of liver fibrosis assessment; however, this procedure is limited by its invasiveness and potential sampling error. Numerous methods for the non-invasive assessment of liver fibrosis have been investigated in the past decade. Transient elastography (TE) is a rapid, non-

invasive, and reproducible method that uses shear wave technology to measure liver stiffness. A high liver stiffness reflects severe liver fibrosis. The use of transient elastography has been extensively validated by numerous investigators in CHB [50]. However, when serum ALT is elevated, TE tends to over-estimate the severity of liver fibrosis, so fibrosis score should be evaluated according to ALT-stratified cutoffs. Recently, bilirubin normalization has been considered important in improving the performance of TE for compensated hepatitis B cirrhosis detection [52]. Furthermore, TE has been confirmed to be valuable for the high-risk prediction of esophageal varices in patients with hepatitis B-related cirrhosis [53]. Accordingly, TE is a reliable tool for detecting severe fibrosis and cirrhosis in patients with CHB. However, validation studies are still needed to identify the other clinical applications of this tool.

Conclusions

Remarkable progress in CHB management has been achieved with the development of new antiviral drugs in the past decade. The introduction of hepatitis B vaccination programs has changed the epidemiology of hepatitis B virus infection in China from highly to moderately endemic. The adoption of good clinical practice and proper conduction of well-designed clinical trials on conventional and pegylated IFNs and NAs has generated important clinical evidence. However, financial burden and drug resistance remain to be the challenges in China. Many treatment issues that are still unsatisfactory or unclear need further investigation. Further studies are needed to clarify how to establish individualized treatment strategy by using the multi-sided predictors in the management of patients in clinical practice.

Acknowledgements

This study was funded by National Science and Technology Major Project (2012ZX10002003).

Abbreviations

ADV	adefovir
ALT	alanine aminotransferase
CHB	chronic hepatitis B
CXCR5	circulating chemokine (C-XC motif) receptor
ETV	entecavir
GWAS	genome-wide association study
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
LAM	lamivudine
LDT	telbivudine
PEG-IFN	pegylated interferons

TDF	tenofovir
TE	transient elastography
NAs	nucleos(t)ide analogs

Compliance with ethics guidelines

Jinlin Hou has received consulting fees from Roche, Novartis, GSK, and Bristol-Myers Squibb and has received grant/research support from Roche, Novartis, and GSK. Rui Yu and Rong Fan declare that they have no conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

- World Health Organization. Hepatitis B. (Revised July 2013). [2010–11–30] <http://www.who.int/mediacentre/factsheets/fs204/en/>
- Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. *N Engl J Med* 2004; 350(11): 1118–1129
- Chan HL, Sung JJ. Hepatocellular carcinoma and hepatitis B virus. *Semin Liver Dis* 2006; 26(2): 153–161
- Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, Zhang Y, Liu J, Gong X, Chen Y, Wang F, Zheng H, Wang F, Guo J, Jia Z, Ma J, Wang H, Luo H, Li L, Jin S, Hadler SC, Wang Y. Epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. *Vaccine* 2009; 27(47): 6550–6557
- Schaefer S. Hepatitis B virus: significance of genotypes. *J Viral Hepat* 2005; 12(2): 111–124
- Zeng G, Wang Z, Wen S, Jiang J, Wang L, Cheng J, Tan D, Xiao F, Ma S, Li W, Luo K, Naoumov NV, Hou J. Geographic distribution, virologic and clinical characteristics of hepatitis B virus genotypes in China. *J Viral Hepat* 2005; 12(6): 609–617
- Wang Z, Liu Z, Zeng G, Wen S, Qi Y, Ma S, Naoumov NV, Hou J. A new intertype recombinant between genotypes C and D of hepatitis B virus identified in China. *J Gen Virol* 2005; 86(Pt 4): 985–990
- Zhou B, Xiao L, Wang Z, Chang ET, Chen J, Hou J. Geographical and ethnic distribution of the HBV C/D recombinant on the Qinghai-Tibet Plateau. *PLoS One* 2011; 6(4): e18708
- Zhou B, Wang Z, Yang J, Sun J, Li H, Tanaka Y, Mizokami M, Hou J. Novel evidence of HBV recombination in family cluster infections in western China. *PLoS One* 2012; 7(6): e38241
- Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; 295(1): 65–73
- European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol* 2012; 57(1): 167–185
- Liaw YF, Kao JH, Piratvisuth T, Chan H, Chien RN, Liu CJ, Gane E, Locarnini S, Lim SG, Han KH, Amarapurkar D, Cooksley G, Jafri W, Mohamed R, Hou JL, Chuang WL, Lesmana L, Sollano J, Suh DJ, Omata M. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatology International* 2012; 6(3): 531–561
- Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; 50(3): 661–662
- Sonneveld MJ, Hansen BE, Piratvisuth T, Jia JD, Zeuzem S, Gane E, Liaw YF, Xie Q, Heathcote EJ, Chan HL, Janssen HL. Response-guided peginterferon therapy in hepatitis B e antigen-positive chronic hepatitis B using serum hepatitis B surface antigen levels. *Hepatology* 2013; 58(3): 872–880
- Hou J, Ma H, Sun J, Xie Q, Xie Y, Sun Y, Wang H, Shi G, Wan M, Niu J, Ning Q, Yu Y, Zhao Y. Response guided peginterferon alfa-2a (PegIFN alfa-2a) therapy in patients with HBeAg-positive chronic hepatitis B (CHB). *J Hepatol* 2014[Epub ahead of print] (abstract)
- Rijckborst V, Hansen BE, Cakaloglu Y, Ferenci P, Tabak F, Akdogan M, Simon K, Akarca US, Flisiak R, Verhey E, Van Vuuren AJ, Boucher CA, ter Borg MJ, Janssen HL. Early on-treatment prediction of response to peginterferon alfa-2a for HBeAg-negative chronic hepatitis B using HBsAg and HBV DNA levels. *Hepatology* 2010; 52(2): 454–461
- Ning Q, Han M, Sun Y, Jiang JJ, Tan D, Hou J, Tang H, Sheng JF, Jiang M. Patients with HBeAg-positive chronic hepatitis B (CHB) with a maintained virological response to entecavir achieved HBsAg clearance when switched to peginterferon alfa-2a therapy (the OSST study). *Hepatology* 2011; 54(Suppl): 1010–1A
- Chan HL. Peginterferon therapy for chronic hepatitis B: one size fits all? *Gut* 2013; 62(2): 185–187
- Tenney DJ, Pokornowski KA, Rose RE, Baldick CJ, Eggers BJ, Fang J, Wichroski MJ, Diva UA, Xu D, Wilber RB, Brett-Smith H, Iloeje UH. 20 entecavir maintains a high genetic barrier to HBV resistance through 6 years in naive patients. *J Hepatol* 2009; 50 (Suppl): S10
- Yokosuka O, Takaguchi K, Fujioka S, Shindo M, Chayama K, Kobashi H, Hayashi N, Sato C, Kiyosawa K, Tanikawa K, Ishikawa H, Masaki N, Seriu T, Omata M. Long-term use of entecavir in nucleoside-naïve Japanese patients with chronic hepatitis B infection. *J Hepatol* 2010; 52(6): 791–799
- Marcellin EJGP, Tsai N, Flisiak R, Petersen SGJ, Kotzev IA, Flaherty JF, Dinh P, Gaggar A, Kitrinis KM, Subramanian M, McHutchison JG, George J, Buti M. Seven years of treatment with tenofovir DF for chronic hepatitis B virus infection is safe and well tolerated and associated with sustained virological, biochemical and serological responses with no detectable resistance. *Hepatology* 2013; 58(S1): 649A
- Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Schall RA, Bornstein JD, Kitrinis KM, Subramanian GM, McHutchison JG, Heathcote EJ. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet* 2013; 381(9865): 468–475
- Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, Dienstag JL, Heathcote EJ, Little NR, Griffiths DA, Gardner SD, Castiglia M. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003; 125(6): 1714–1722
- Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, Lim SG, Goodman Z, Ma J, Brosgart CL, Borroto-Esoda K, Arterburn S, Chuck SL; Adefovir Dipivoxil 438 Study Group. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006; 131(6): 1743–1751

25. Yuen MF, Sablon E, Hui CK, Yuan HJ, Decraemer H, Lai CL. Factors associated with hepatitis B virus DNA breakthrough in patients receiving prolonged lamivudine therapy. *Hepatology* 2001; 34(4): 785–791
26. Chae HB, Hann HW, Hui CK, Yuan HJ, Decraemer H, Lai CL. Baseline HBV DNA level is the most important factor associated with virologic breakthrough in chronic hepatitis B treated with lamivudine. *World J Gastroenterol* 2007; 13(30): 4085–4090
27. Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, Heathcote EJ, Manns M, Bzowej N, Niu J, Han SH, Hwang SG, Cakaloglu Y, Tong MJ, Papatheodoridis G, Chen Y, Brown NA, Albanis E, Galil K, Naoumov NV; GLOBE Study Group. 2-Year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009; 136(2): 486–495
28. Hann HW. Telbivudine: an effective anti-HBV drug for chronic hepatitis B patients with early on-treatment responses. *Expert Opin Pharmacother* 2010; 11(13): 2243–2249
29. Sung JJ, Lai JY, Zeuzem S, Chow WC, Heathcote EJ, Perrillo RP, Brosgart CL, Woessner MA, Scott SA, Gray DF, Gardner SD. Lamivudine compared with lamivudine and adefovir dipivoxil for the treatment of HBeAg-positive chronic hepatitis B. *J Hepatol* 2008; 48(5): 728–735
30. Hui CK, Zhang HY, Bowden S, Locarnini S, Luk JM, Leung KW, Yueng YH, Wong A, Rousseau F, Yuen KY, Naoumov NN, Lau GK. 96 weeks combination of adefovir dipivoxil plus emtricitabine vs. adefovir dipivoxil monotherapy in the treatment of chronic hepatitis B. *J Hepatol* 2008; 48(5): 714–720
31. Lok AS, Trinh H, Carosi G, Akarca US, Gadano A, Habersetzer F, Sievert W, Wong D, Lovegren M, Cohen D, Llamoso C. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naïve patients with chronic hepatitis B. *Gastroenterology* 2012; 143(3): 619–28 e1
32. Terrault NA. Benefits and risks of combination therapy for hepatitis B. *Hepatology* 2009; 49(5 Suppl): S122–S128
33. Keeffe EB, Zeuzem S, Koff RS, Dieterich DT, Esteban-Mur R, Gane EJ, Jacobson IM, Lim SG, Naoumov N, Marcellin P, Piratvisuth T, Zoulim F. Report of an international workshop: roadmap for management of patients receiving oral therapy for chronic hepatitis B. *Clin Gastroenterol Hepatol* 2007; 5(8): 890–897
34. Sun J, Xie Q, Tan D, Ning Q, Niu J, Bai X, Fan R, Chen S, Cheng J, Yu Y, Wang H, Xu M, Shi G, Wan M, Chen X, Tang H, Sheng J, Dou X, Shi J, Ren H, Wang M, Zhang H, Gao Z, Chen C, Ma H, Jia J, Hou J. The 104-week efficacy and safety of telbivudine-based optimization strategy in chronic hepatitis B patients: a randomized, controlled study. *Hepatology* 2014; 59(4): 1283–1292
35. Peters MG, Hann HW, Martin P, Heathcote EJ, Buggisch P, Rubin R, Bourliere M, Kowdley K, Treppe C, Gray DF, Sullivan M, Kleber K, Ebrahimi R, Xiong S, Brosgart CL. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology* 2004; 126(1): 91–101
36. Rapti I, Dimou E, Mitsoula P, Hadziyannis SJ. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B. *Hepatology* 2007; 45(2): 307–313
37. Lampertico P, Viganò M, Manenti E, Iavarone M, Sablon E, Colombo M. Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. *Gastroenterology* 2007; 133(5): 1445–1451
38. Yang H, Qi X, Sabogal A, Miller M, Xiong S, Delaney WE 4th. Cross-resistance testing of next-generation nucleoside and nucleotide analogues against lamivudine-resistant HBV. *Antivir Ther* 2005; 10(5): 625–633
39. Lada O, Benhamou Y, Cahour A, Katlama C, Poynard T, Thibault V. *In vitro* susceptibility of lamivudine-resistant hepatitis B virus to adefovir and tenofovir. *Antivir Ther* 2004; 9(3): 353–363
40. Sun J, Hou JL, Xie Q, Li XH, Zhang JM, Wang YM, Wang H, Lai JY, Chen SJ, Jia JD, Sheng JF, Chan HL, Wang JF, Li MK, Jiang M, Popescu M, Sung JJ. Randomised clinical trial: efficacy of peginterferon alfa-2a in HBeAg positive chronic hepatitis B patients with lamivudine resistance. *Aliment Pharmacol Ther* 2011; 34(4): 424–431
41. Berg T, Marcellin P, Zoulim F, Moller B, Trinh H, Chan S, Suarez E, Lavocat F, Snow-Lampart A, Frederick D, Sorbel J, Borroto-Esoda K, Oldach D, Rousseau F. Tenofovir is effective alone or with emtricitabine in adefovir-treated patients with chronic-hepatitis B virus infection. *Gastroenterology* 2010; 139(4): 1207–1217, e3
42. Sherman M, Yurdaydin C, Sollano J, Silva M, Liaw YF, Cianciara J, Boron-Kaczmarek A, Martin P, Goodman Z, Colonna R, Cross A, Denisky G, Kreter B, Hinder R; AI463026 BEHoLD Study Group. Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. *Gastroenterology* 2006; 130(7): 2039–2049
43. Sherman M, Yurdaydin C, Simsek H, Silva M, Liaw YF, Rustgi VK, Sette H, Tsai N, Tenney DJ, Vaughan J, Kreter B, Hinder R; AI463026 Benefits of Entecavir for Hepatitis B Liver Disease (BEHoLD) Study Group. Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. *Hepatology* 2008; 48(1): 99–108
44. Petersen J, Ratziu V, Buti M, Janssen HL, Brown A, Lampertico P, Schollmeyer J, Zoulim F, Wedemeyer H, Sterneck M, Berg T, Sarrazin C, Lutgehetmann M, Buggisch P. Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: an international multicenter cohort study. *J Hepatol* 2012; 56(3): 520–526
45. Chotiayaputta W, Peterson C, Ditah FA, Goodwin D, Lok AS. Persistence and adherence to nucleos(t)ide analogue treatment for chronic hepatitis B. *J Hepatol* 2011; 54(1): 12–18
46. Domingo E. Viruses at the edge of adaptation. *Virology* 2000; 270(2): 251–253
47. Rodriguez C, Chevaliez S, Bensadoun P, Pawlotsky JM. Characterization of the dynamics of hepatitis B virus resistance to adefovir by ultra-deep pyrosequencing. *Hepatology* 2013; 58(3): 890–901
48. Ma SW, Huang X, Li YY, Tang LB, Sun XF, Jiang XT, Zhang YX, Sun J, Liu ZH, Abbott WG, Dong YH, Naoumov NV, Hou JL. High serum IL-21 levels after 12 weeks of antiviral therapy predict HBeAg seroconversion in chronic hepatitis B. *J Hepatol* 2012; 56(4): 775–781
49. Li Y, Ma S, Tang L, Li Y, Wang W, Huang X, Lai Q, Zhang M, Sun J, Li CK, Abbott WG, Naoumov NV, Zhang Y, Hou J. Circulating chemokine (C-X-C Motif) receptor 5(+) CD4(+) T cells benefit hepatitis B e antigen seroconversion through IL-21 in patients with chronic hepatitis B virus infection. *Hepatology* 2013; 58(4): 1277–1286
50. Wong VW, Chan HL. Transient elastography. *J Gastroenterol*

- Hepatology 2010; 25(11): 1726–1731
51. Chan HL, Wong GL, Choi PC, Chan AW, Chim AM, Yiu KK, Chan FK, Sung JJ, Wong VW. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. *J Viral Hepat* 2009; 16(1): 36–44
52. Chen YP, Liang XE, Dai L, Zhang Q, Peng J, Zhu YF, Wen WQ, Chan HL, Hou JL. Improving transient elastography performance for detecting hepatitis B cirrhosis. *Dig Liver Dis* 2012; 44(1): 61–66
53. Chen YP, Zhang Q, Dai L, Liang XE, Peng J, Hou JL. Is transient elastography valuable for high-risk esophageal varices prediction in patients with hepatitis-B-related cirrhosis? *J Gastroenterol Hepatol* 2012; 27(3): 533–539