World Journal of Hepatology

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DOI: 10.4254/wjh.v7.i11.1541

World J Hepatol 2015 June 18; 7(11): 1541-1552
ISSN 1948-5182 (online)

REVIEW

Current and future directions for treating hepatitis B virus infection

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Author contributions: Tawada A, Kanda T and Yokosuka O contributed to this paper.

Conflict-of-interest: Akinobu Tawada has no conflict of interest to declare. Tatsuo Kanda reports receiving lecture fees from Chugai Pharmaceutical, MSD, Tanabe-Mitsubishi, Daiichi-Sankyo, and Bristol-Myers Squibb, and Osamu Yokosuka reports receiving grant support from Chugai Pharmaceutical, Bayer, MSD, Daiichi-Sankyo, Tanabe-Mitsubishi, and Bristol-Myers Squibb.

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Received: January 10, 2015
Peer-review started: January 10, 2015
First decision: March 6, 2015
Revised: March 16, 2015
Accepted: April 28, 2015
Article in press: April 30, 2015
Published online: June 18, 2015

Abstract

Hepatitis B virus (HBV) persistently infects approximately 350 million people, and approximately 600000 liver-related deaths are observed per year worldwide. HBV infection is also one of the major risk factors for hepatocellular carcinoma (HCC). The persistence of serum hepatitis B e antigen (HBeAg) and high level of serum HBV DNA are thought to reflect a high HBV replication status in hepatocytes, causing cirrhosis, HCC and liver-related deaths. It has been reported that antiviral therapy, such as peginterferon and nucleos(t)ide analogues (NUCs), could suppress liver-related death by inhibiting the HBV DNA levels and inducing seroconversion from HBeAg to antibody to HBe antigen. Currently, peginterferon is widely used, but there are also several disadvantages in the use of peginterferon, such as various adverse events, the administration route and duration. It is difficult to predict the effects of treatment and interferon is contraindicated for the patients with advanced fibrosis of the liver and cirrhosis. With respect to NUCs, entecavir and tenofovir disoproxil fumarate are current the first-choice drugs. NUCs can be administered orally, and their anti-viral effects are stronger than that of peginterferon. However, because cessation of NUC administration leads to high levels of viral replication and causes severe hepatitis, they must be administered for a long time. On the other hand, the use of both interferon and NUCs cannot eliminate covalently closed circular DNA of HBV. In this review, we evaluate the natural course of chronic HBV infection and then provide an outline of these representative drugs, such as peginterferon, entecavir and tenofovir disoproxil fumarate.

Key words: Hepatocellular carcinoma; Peginterferon; Nucleotide analogue; Chronic hepatitis B

Core tip: Chronic hepatitis B virus (HBV) infection is one of the major causes of hepatocellular carcinoma, which is a cancer with poor prognosis. We reviewed the natural

course of HBV infection and current standard therapies for chronic HBV infection. Peginterferon and nucleos(t)ide analogues, such as entecavir and tenofovir disoproxil fumarate, have several drug-specific advantages and disadvantages. It is difficult to eliminate covalently closed circular DNA of HBV with these current standard therapies. Further improvements of the therapeutic options for HBV infections should be needed.

Tawada A, Kanda T, Yokosuka O. Current and future directions for treating hepatitis B virus infection. *World J Hepatol* 2015; 7(11): 1541-1552 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i11/1541.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i11.1541

INTRODUCTION

Approximately 350 million people are persistently infected with hepatitis B virus (HBV) and there are 600000 HBV-related deaths annually worldwide[1]. It has been reported that more than 90% of patients infected with HBV in their infancy or childhood become chronic HBV carriers[1]. Of them, approximately 15%-40% develop chronic hepatitis B. In the patients with chronic hepatitis B, approximately 90% could achieve seroconversion of hepatitis B e antigen (HBeAg) to antibody to HBe antigen (anti-HBe) and become inactive carriers. However, approximately 10% of patients with chronic hepatitis B have chronic active hepatitis and develop cirrhosis at a rate of approximately 2% per year, leading to liver failure and/or hepatocellular carcinoma (HCC)[2-5]. Globally, HBV infection is one of the major risk factors of HCC, and it accounts for up to 50% of all HCC patients. Positive serum HBeAg and a high level of serum HBV DNA are indicative of high HBV replication in the liver[6-8]. Therefore, it is important to suppress HBV replication to prevent hepatic failure and the development of cirrhosis and HCC. To prevent the disease progression, peginterferon and nucleos(t)ide analogues (NUCs) are now available as antivirals against HBV[9-12].

In general, the natural history of chronic HBV infection in birth or early childhood is divided into five phases as follows (Figure 1). In phase 1 (immune tolerance phase/asymptomatic carrier phase), HBV is actively replicating, but the host lacks an immune response. The serum alanine aminotransferase (ALT) level is within the normal limit and liver inflammation is almost absent. In phase 2 (immune clearance phase), in adulthood, the immune response to HBV becomes active, and an elevated serum ALT level and active hepatitis are observed. In phase 3 (inactive phase), as a result of an immune response, HBeAg is lost, anti-HBe emerges, the serum HBV DNA level is suppressed and liver inflammation is low[13]. Some patients cannot achieve seroconversion from HBeAg to anti-HBe and HBeAg persists as positive. For most of those with positive HBeAg, active hepatitis persists, and they often rapidly proceed to cirrhosis (HBeAg-positive hepatitis). In approximately 10%-20% of HBeAg-negative carriers, HBV DNA replication is reactivated and active hepatitis flares again (HBeAg-negative hepatitis) (phase 4)[14]. It should be noted that there are some developments in HCC even at low rates in this phase[15]. For approximately 4% to 20% of HBeAg-negative carriers, anti-HBe is lost and HBeAg reappears again (reverse seroconversion). In the natural course of HBeAg-negative carriers, HBs antigen (HBsAg) converts to negative and antibody to HBs antigen (anti-HBs) develops at a rate of 1% per year (phase 5, remission phase). In this phase, the both blood test and liver histology findings might be improved.

For acute-on-chronic liver failure and HCC, the risk factors are obvious and antiviral therapies could reduce the risk of developing acute-on-chronic liver failure and HCC[16]. In general, the indication and selection of antiviral therapies for persistent HBV infection is decided according to the age, disease phase, fibrosis stage and inflammatory activity of the liver, and risk of disease progression. In the immune tolerance phase, the rate of HBV clearance from the hepatocytes is very low because of the lack of a host immune response. In the low replication phase (inactive carriers), antiviral therapy may not be indicated if the liver histological findings are mild and the serum ALT level is within normal limits. In the remission phase (negative HBsAg), if HBV DNA is not detected, antiviral therapy may not be indicated because hepatitis calms down and the HCC development rates decrease[17] while NUC administration may be stopped. In young patients with HBeAg-positive chronic hepatitis and elevated serum ALT levels, there is a 7%-16% possibility of HBeAg-negative conversion. Then, strict observation without treatment may be chosen if there is no advanced fibrosis or possibility of fulminant hepatitis[16].

HBV-INFECTED PATIENTS WITH CIRRHOSIS

While cirrhotic patients are thought to be therapeutic indication even if HBeAg is negative, the serum ALT level is normal and serum HBV DNA level is suppressed at a low level. If advanced fibrosis is clinically suspected, the assessment of fibrosis should be performed by liver biopsy, abdominal ultrasonography, elastography or abdominal computed tomography[18-22]. If advanced fibrosis is observed, antiviral therapy should be started. HBV carriers who are not asymptomatic or inactive carriers are indicated to receive antiviral therapy, and inactive carriers with advanced fibrosis and a high serum HBV DNA level are also indicated to receive antiviral therapy.

At present, the complete elimination of covalently closed circular DNA (cccDNA) in nucleus of liver cells[23] seems difficult using peginterferon and NUCs. The best surrogate markers for antiviral treatment against HBV

Table 1 Treatment efficacy at 24 wk after the end of peginterferon treatment in hepatitis B e antigen-positive chronic hepatitis B

Ref.	No. of patients	Formula of therapy	Seroconversion from HBeAg to anti-HBe (%)	Suppression of HBV DNA (%)	Normalization of ALT (%)	HBsAg loss (*n*)
Cooksley *et al*[27]	51	IFNα-2a 4.5 MIU three times weekly for 24 wk	25	25[a]	26	0
	49	Peg-IFNα-2a 90 μg weekly for 24 wk	37	43[a]	43	0
	46	Peg-IFNα-2a 180 μg weekly for 24 wk	35	39[a]	35	0
	48	Peg-IFNα-2a 270 μg weekly for 24 wk	27	27[a]	31	0
Lau *et al*[28]	214	Peg-IFNα-2a 180 μg weekly plus placebo for 48 wk	32	32[b]	41	8
	271	Peg-IFNα-2a 180 μg weekly plus LAM 100 mg daily for 48 wk	27	34[b]	39	8
	272	LAM 100 mg/d for 48 wk	19	22[b]	28	0
Chan *et al*[29]	50	Peg-IFNα-2b 1.5 μg/kg weekly for 32 wk plus LAM 100 mg daily for 52 wk	36	36[a]	50	1
	50	LAM 100 mg daily for 52 wk	14	14[a]	30	0
Liaw *et al*[30]	140	Peg-IFNα-2a 90 μg weekly for 24 wk	14	21[c]	30	1
	136	Peg-IFN α-2a 180 μg weekly for 24 wk	22	21[c]	30	0
	136	Peg-IFNα-2a 90 μg weekly for 48 wk	25	32[c]	43	3
	136	Peg-IFNα-2a 180 μg weekly for 48 wk	36	42[c]	52	3

a < 500000 copies/mL; b < 100000 copies/mL; c < 20000 copies/mL. LAM: Lamivudine; Peg-IFN: Peginterferon; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; Anti-HBe: Antibody to HBe antigen; ALT: Alanine aminotransferase.

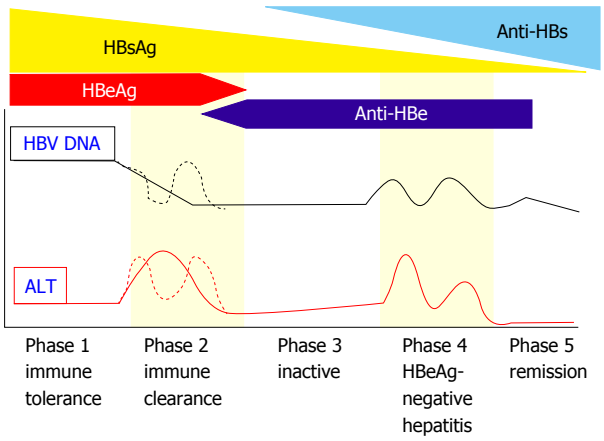

Figure 1 Natural course of hepatitis B virus infection[116]. HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBsAg: Hepatitis B s antigen; Anti-HBe: Antibody to HBe antigen; Anti-HBs: Antibody to HBs antigen.

are HBsAg as a long-term marker as well as sustained normalization of the serum ALT level, negative serum HBV DNA level and negative HBeAg as short-term markers[16].

PEGINTERFERON THERAPY

Greenberg *et al*[24] reported the usefulness of interferon therapy for chronic hepatitis B in 1976. Interferon exerts antiviral activity, cell growth inhibition and immunomodulatory effects. It binds to the interferon receptors of hepatocytes, activates tyrosine type protein kinase Janus kinase 1 and induces phosphorylation and dimerization of signal transducer and activator of transcription 1 (STAT1). The STAT1 dimer translocates into the nucleus, induces interferon stimulated genes, and expresses various antiviral proteins that have antiviral effects[25]. The HBeAg-negative conversion rate of the interferon treated group was significantly higher than that of the untreated control group[26]. Interferon is non-antigen specific immunomodulator. Compared with NUCs, one of the advantages of interferon is that its treatment duration is limited and its effect is durable. The other benefit of interferon is that there is no risk of resistance mutants. However, interferon has no direct inhibitory effect on viral replication and its short-term effect, such as suppressing serum HBV DNA level, is inferior to NUCs. The other disadvantage of interferon is the difficulty in predicting the treatment effect and several adverse events, such as flu-like syndrome. Additionally, it is difficult to use interferon on patients with advanced liver fibrosis and cirrhosis.

Compared to standard interferon, peginterferon-alpha has a long half-life and gains its long-acting effect through the addition of polyethylene glycol high molecular proteins to interferon. Its administration is performed only once per week. There have been several reports about peginterferon for HBeAg-positive or HBeAg-negative patients (Tables 1-3)[27-35]. In the comparison trial with standard interferon-alpha and peginterferon-alpha in Asia, the combined responses, defined as HBeAg loss, HBV DNA suppression (< 500000 copies/mL) and ALT normalization, were 28% *vs* 12%, respectively (P = 0.036), and the superiority of peginterferon-alpha to standard interferon has been demonstrated[27]. A report comparing three groups of 48 wk of peginterferon-alpha-2a alone, 48 wk of peginterferon-alpha2a plus lamivudine, and 48 wk of lamivudine alone in 814 HBe positive patients reported that the HBeAg seroconversion rates 24 wk after the end of administration were 32%, 27% and 19%, respectively, and the peginterferon-alpha-2a alone group had a significantly higher effect than lamivudine alone group[28]. The HBsAg-negative

Table 2 Long-term treatment efficacy of peginterferon treatment in hepatitis B e antigen-positive chronic hepatitis B

Ref.	No. of patients	Formula of therapy	Seroconversion from HBeAg to anti-HBe (%)	Suppression of HBV DNA (%)	Normalization of ALT (%)	HBsAg loss (*n*)
[c]Buster *et al*[31]	91	Peg-IFNα-2b for 52 wk	35	25[a]	30	7 (8%)
	81	Peg-IFNα-2b plus LAM for 52 wk	25	31[a]	30	12 (15%)
[d]Wong *et al*[32]	85	Peg-IFNα-2b for 32 wk plus LAM for 52 or 104 wk	60	13[b]	57	2 (2.4%)

a < 10000 copies/mL; b < 100 copies/mL. The treatment efficacies were assessed at approximately 3-year follow-up[c] or approximately 5-year follow-up[d]. LAM: Lamivudine; Peg-IFN: Peginterferon; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; ALT: Alanine aminotransferase.

Table 3 Treatment efficacy of peginterferon treatment in hepatitis B e antigen-negative chronic hepatitis B

Ref.	No. of patients	Therapy regimen	HBV DNA suppression (%)	ALT normalization (%)	HBsAg loss (*n*)
[c]Marcellin *et al*[33]	177	Peg-IFNα-2a 180 μg weekly plus placebo for 48 wk	43[a]	59	7
	179	Peg-IFNα-2a 180 μg weekly plus LAM 100 mg daily for 48 wk	44[a]	60	5
	181	LAM 100 mg daily for 48 wk	29[a]	44	0
[c]Papadopoulos *et al*[34]	88	Peg-IFNα-2b 1.5 μg/kg weekly plus LAM 100 mg daily for 48 wk	59 (60 IU/mL below)	27	NA
	35	Peg-IFNα-2b 1.5 μg/kg weekly for 48 wk	42	40	NA
[d]Marcellin *et al*[35]	116	Peg-IFNα-2a 180 μg weekly plus placebo for 48 wk	28[b]	31	9 (8%)
	114	Peg-IFNα-2a 180 μg daily plus LAM 100 mg daily for 48 wk	25[b]	31	9 (8%)
	85	LAM 100 mg daily for 48 wk	15[b]	18	0 (0%)

a < 20000 copies/mL; b < 10000 copies/mL. The treatment efficacies were assessed at 24-wk follow-up[c] or approximately 3-year follow-up[d]. LAM: Lamivudine; Peg-IFN: Peginterferon; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; NA: Not available.

conversion rate was 3%[28]. In a NEPTUNE trial exploring the appropriate dose and duration of interferon treatment, the HBeAg seroconversion rate of 180 μg peginterferon-alpha-2a for 48 wk was significantly higher than that of 24 wk or 90 μg. Therefore, 180 μg peginterferon-alpha-2a administrations for 48 wk were considered the standard treatment[30]. The durable effect after stopping (peg)interferon administration is one specific advantage of this therapy. In another report[31], 81% of HBeAg-positive patients who achieved HBeAg-negative conversion by peginterferon-alpha-2b sustained their effect at years 3 after stopping interferon administration, and 27% of patients who could not achieve HBeAg-negative conversion at week 26 achieved HBeAg-negative conversion at years 3 (Table 2)[31]. In that report[31], 11% of all patients and 30% of patients who achieved HBeAg-negative conversion at month 6 achieved HBsAg-negative conversion even though 31% of all patients in this trial were genotype A and 47% were given additional NUCs. In a multicenter, randomized control trial conducted in Europe on peginterferon-alpha-2a for HBeAg-negative patients comparing three groups treated with 48 wk of peginterferon-alpha-2a alone, 48 wk of peginterferon-alpha-2a plus lamivudine and 48 wk of lamivudine alone, the serum ALT normalization rates 24 wk after end of administration were 59%, 60% and 44% and the serum HBV DNA negative rates were 43%, 44% and 29%, respectively (Table 3)[33]. HBsAg converted to negative in 7 patients in the peginterferon-alpha-2a alone group and 5 patients in the peginterferon-alpha-2a plus lamivudine group. A meta-analysis comparing peginterferon with NUCs has already been published and it was reported that peginterferon-alpha achieved a higher serum HBsAg-negative conversion rate compared to lamivudine monotherapy[36]. In a European multicenter trial conducted over 3 years, 8.7% of all patients and 44% of HBV DNA-negative patients treated with peginterferon-alpha-2a alone had HBsAg-negative conversion[35]. For a longer duration of peginterferon administration in HBeAg-negative patients, 180 μg of peginterferon-alpha-2a administered for 48 wk or 96 wk (49 wk or later, the peginterferon dose was down to 135 μg) were compared and the serum HBV DNA suppression rates (< 2000 IU/mL) were 29% *vs* 12% and serum HBsAg-negative conversion rates were 0% *vs* 6%, respectively. Also, the 96 wk administration was superior to 48 wk administration[37]. Patients in this study were infected with HBV genotype D. The HBeAg-negative patients treated by peginterferon-alpha-2a had worse results than HBeAg-positive patients treated by the same regimen.

While the prediction of the treatment effect by pre-treatment factors is difficult for (peg)interferon therapy, some reports have showed that measuring the serum HBsAg level at weeks 12, 24 and 48 after starting interferon administration contributed to predicting the therapeutic response (HBeAg seroconversion, HBV DNA-negative conversion and HBsAg-negative conversion) for both HBeAg-negative and HBeAg-positive patients[38,39].

Table 4 Treatment efficacy of entecavir in chronic hepatitis B

Ref.	No. of patients	HBeAg	Therapy regimen	HBeAg loss (%)/seroconversion from HBeAg to anti-HBe (%)	Undetectable of HBV DNA (%)	Normalization of ALT (%)	HBsAg loss (*n*)
[1]Chang *et al*[66]	354 NUCs - treatment-naive	Positive	ETV 0.5 mg daily for 48 wk	22/21	67	68	6
	355 NUCs - treatment-naive	Positive	LAM 100 mg daily for 48 wk	20/18	36	60	4
[2]Gish *et al*[67]	243 NUCs - treatment-naive	Positive	ETV 0.5 mg daily for 2 yr	NA/31	80	87	18
	164 NUCs - treatment-naive	Positive	LAM 100 mg daily for 2 yr	NA/26	39	79	10
[1]Lai *et al*[70]	296	Negative	ETV 0.5 mg daily for 48 wk	NA/NA	90	78	1
	287	Negative	LAM 100 mg daily for 48 wk	NA/NA	72	71	1

Treatment efficacies were assessed at 48 wk[1], or 2 years[2]. ETV: Entecavir; NUCs: Nucleos(t)ide analogues; NA: Not available; LAM: Lamivudine; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBsAg: Hepatitis B surface antigen; Anti-HBe: Antibody to HBe antigen.

With respect to the factors affecting the outcome of interferon therapy, the HBV genotype[40-42], age[43] and fibrosis of the liver[44] were reported to affect the therapeutic outcome of standard interferon. On the other hand, peginterferon is highly effective and the age and HBV genotypes are no longer related to the treatment effect of peginterferon except for HBV genotype A[45,46]. For the other HBV genotypes, the therapeutic effects of genotypes C and B for HBeAg-positive and HBeAg-negative patients have been reported to be equivalent[28,35,47-49]. The pretreatment level of HBsAg could not predict the treatment effect, but its reduction rate and level during treatment can predict the therapeutic effect for both HBeAg-positive[39,50] and HBeAg-negative patients[48,51], and it is thought to be useful marker for predicting the therapeutic effect. Additionally, older age is not reported to be related to the therapeutic effect with current peginterferon[30,46], whereas it has been reported that older age has a favorable effect for HBeAg-positive patients[45,52]. Also, advanced fibrosis of the liver was reported to affect treatment response with current peginterferon for chronic hepatitis B[53]. It was reported that the interleukin-28B (*IL28B*) genotypes affected the HBeAg seroconversion and HBsAg-negative conversion rates[52], although the impact of the *IL28B* gene on the treatment effect of interferon is controversial.

Interferon has immunostimulatory action, and it is generally necessary to consider the acute exacerbation risk of hepatitis by immunological destruction of HBV infected cells, especially for cirrhotic patients. Therefore, interferon therapy is thought to be contraindicated for HBV-related cirrhosis.

NUCS

NUCs specifically inhibit DNA polymerase that HBV DNA itself produces in the reverse transcription process of HBV replication. NUCs strongly inhibit the synthesis of the plus and minus strand chains in the HBV life cycle. The effect is highly specific and efficient. All NUCs can be administered orally and their use is simple. The short-term adverse events of NUCs are rare and mild, and they are effective for either genotype. Furthermore, unlike interferon, they are easy for cirrhotic patients to use. On the other hand, HBV cannot be completely eliminated because NUCs cannot eliminate mRNA or cccDNA in the host nucleus, which acts as a template for HBV DNA.

Once NUC administration is stopped, HBV DNA starts to reappear or increase, and hepatitis recurs in some patients[54-58]. Additionally, HBeAg that is negatively converted by NUC administration frequently re-appears when NUC administration is stopped (reverse seroconversion)[59,60] after a flare of severe hepatitis[61]. There have been several reports that NUC contributes to HBsAg-negative conversion[62-65]. To improve the long-term prognosis of patients, continuous administration of NUCs for long-term HBV suppression is necessary. Here we focus especially on entecavir and tenofovir disoproxil fumarate (tenofovir), which are now available as first line drugs for chronic hepatitis B in many countries.

Entecavir

Previous reports about entecavir treatment are summarized in Table 4[66-76]. The serum HBV DNA-negative conversion and serum ALT normalization rates of entecavir for 48 to 96 wk were superior to those in response to lamivudine for both HBeAg-positive and HBeAg-negative patients[66,67,70,77]. With entecavir administration for 3 to 5 years, the serum HBV DNA-negative conversion rates were 55% to 88%/1 year, 83% to 93%/2 years, 89% to 95%/3 years, and 91% to 96%/4 years, 94%/5 years; the serum ALT normalization rates were 65% to 84%/1 year, 78% to 88%/2 years, 77% to 90%/3 years, 86%/4 years, and 80%/5 years; and the HBeAg seroconversion rates were 12% to 22%/1 year, 18% to 41%/2 years, 29% to 44%/3 years and 38%/4 years[69,74-76,78]. The resistance mutant emergence rates were reported to be 0.2%/1 year, 0.5%/2 years, and 1.2%/3 to 5 years for the NUCs-treatment-naive patients[69,78].

Today, entecavir is one of the first line NUCs for NUC-treatment-naive patients as well as tenofovir in many countries. However, the serum HBsAg-negative

Table 5 Treatment efficacy of tenofovir in chronic hepatitis B

Ref.	No. of patients	HBeAg	Therapy regimen	HBeAg loss (%)/seroconversion from HBeAg to anti-HBe (%)	Undetectable of HBV DNA (%)	Normalization of ALT (%)	HBsAg loss (*n*)
[1]Marcellin *et al*[83]	176 NUCs - treatment-naive	Positive	TDF 300 mg daily (> 48 wk)	NA/21	76	68	5
	90	Positive	ADF 10 mg daily (> 48 wk)	NA/18	13	54	0
	90	Positive	ADF (48 wk)	NA/18	13	54	0
	125	Negative	ADF (48 wk)	NA/NA	63	77	0
[2]Heathcote *et al*[88]	266	Positive	TDF (> 144 wk)	34/26	71	74	20
	365	Negative	TDF (> 144 wk)	NA/NA	87	81	0
[2]Marcellin *et al*[91]	266	Positive	TDF (> 240 wk)	49/40	65	73	10
	375	Negative	TDF (> 240 wk)	NA/NA	83	85	1

The treatment efficacies were assessed at 48 wk[1], or 144 wk[2]. TDF: Tenofovir; ADF: Adefovir; NA: Not available; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBsAg: Hepatitis B s antigen; Anti-HBe: Antibody to HBe antigen.

conversion is very rare compared with peginterferon and was reported to be 0 to 5.1%/3 to 5 years and 10%/10 years[69,78].

In general, the patients treated with lamivudine and sustained negative HBV DNA are recommended to switch to entecavir or tenofovir. It has been reported that, if the serum HBV DNA level stays negative and there are no resistance mutants during lamivudine administration, entecavir-resistance mutants rarely emerge even when patients are switched to entecavir[79]. Entecavir resistance easily occurs in lamivudine-resistance mutants (rtL180M plus rtM204V) by adding only one more mutation (rt184G, rtS202I or rtM250V) and these states are thought as a low genetic barrier[80]. On the other hand, tenofovir and adefovir lack cross-resistance to entecavir-resistance (rt184G/S, rtS202G/I, M250V)[81]. Therefore, patients who have viral breakthrough under lamivudine administration could easily have entecavir-resistance mutants if they are switched to entecavir, and adding adefovir to lamivudine is generally recommended. Like lamivudine, entecavir was also reported to have a suppressive effect to HCC development compared with the control, and the reported HCC development rates for entecavir *vs* control were 3.7%/5 years *vs* 13.7%/5 years, respectively[10]. The United States Food and Drug Administration (FDA) assigned entecavir to pregnancy category C. Entecavir should not be used for the patients who are co-infected with human immunodeficiency virus (HIV) because of the risk of resistance mutant emergence in HIV.

Tenofovir disoproxil fumarate (tenofovir)

Similar to adefovir, tenofovir is categorized as an acyclic nucleoside phosphonate diester derivative from adenosine monophosphate. Tenofovir has also an antiviral effect against HIV. The usual dosage of tenofovir is 300 mg once a day and higher than that of adefovir 10 mg once a day, owing to the lower nephron-toxicity of tenofovir. The results of tenofovir treatment are shown in Table 5[82-93]. Several reports comparing adefovir 10 mg/d *vs* tenofovir 300 mg/d for NUC-naïve patients reported that the serum HBV DNA suppression rates (< 400 copies/mL) 48 wk after start of administration were 76% *vs* 13% for HBeAg-positive patients and 93% *vs* 63% for HBeAg-negative patients, respectively; also, in general, tenofovir has been superior to adefovir[83]. A study with 144 wk of follow up showed that the serum HBV DNA suppression rates (< 400 copies/mL) were 87% for HBeAg-positive patients and 72% in HBeAg-negative patients at week 144[88]. A 5-year study showed that tenofovir achieved a higher HBsAg-negative conversion rate compared to other NUCs[91].

A recent report with 288 wk of follow up suggested that no apparent resistance mutations were observed[94]. For decompensated cirrhosis, the combination of tenofovir with emtricitabine was reported to achieve positive results[89]. With tenofovir treatment, the serum HBV DNA-negative conversion rate for patients without adefovir-resistance was 100%, but the rate was down to 52% for patients with adefovir-resistance[89]. An important feature of tenofovir is that tenofovir alone or with emtricitabine exerts an anti-viral effect to lamivudine, adefovir or entecavir resistance mutants[85,86,93,95,96]. For example, an article reported that for patients who achieved an insufficient effect by lamivudine, adefovir or the combination of these two drugs, tenofovir resulted in a serum HBV DNA-negative conversion rate of 79%, HBeAg-negative conversion rate of 24% and HBsAg-negative conversion rate of 3% of all patients (the median time from administration to HBsAg-negative conversion was 23 mo)[86]. For patients who achieved insufficient effect by lamivudine and adefovir, tenofovir alone or with lamivudine achieved a 64% serum HBV DNA-negative conversion rate 96 wk after changing therapy[93]. They also reported that they did not observe an obvious resistance mutant[93].

It has been reported that the long-term administration of NUCs improves liver fibrosis. Tenofovir treatment resulted in improvement of the histological findings in 87% of all patients and improvement of liver fibrosis in 51% of all patients[91]. They also reported that 10% of HBeAg-positive patients achieved HBsAg-negative conversion, and most of them were genotype A or D[91]. Tenofovir is only classified as pregnancy category B by the United States FDA.

Table 6 Summary of current and future treatments for hepatitis B virus infection

Current treatments for HBV
Peginterferon therapy
NUCs
Entecavir
Tenofovir disoproxil fumarate (tenofovir)
Future treatments for HBV
NUCs
Tenofovir alafenamide
Treatments for HBV cccDNA
Entry inhibitors targeting of sodium taurocholate cotransporting polypeptide

NUCs: Nucleos(t)ide analogues; HBV: Hepatitis B virus; cccDNA: Covalently closed circular DNA.

Stoppage of entecavir or tenofovir

Apart from interferon, with the use of NUCs such as entecavir and tenofovir, it is always possible for resistant mutants to emerge[97-101]. Suzuki *et al*[101] reported that 51-year-old Japanese women with chronic hepatitis B and cirrhosis have virological breakthrough during combination therapy with tenofovir and entecavir against entecavir-resistant virus. Even long-term therapy with tenofovir against the entecavir-resistant virus has the potential to induce virological breakthrough and resistance. We also reported that virological breakthrough during NUC therapies is also dependent on the adherence to medication[99,100]. In treatment with stronger NUCs, such as entecavir, viral breakthrough associated with poor adherence could be a more important issue[102]. Although we do not know whether durable control of HBV is observed after NUCs are discontinued, NUCs could possibly be stopped in selected patients without causing advanced liver fibrosis.

Adefovir or tenofovir-related Fanconi syndrome is a severe adverse event that results from proximal renal tubular toxicity, which leads to impaired re-absorption of amino acids, uric acid, bicarbonate, glucose and phosphate associated with the increased urinary excretion of these solutes[103-106]. Some cases associated with Fanconi syndrome induced by NUCs-treatment were fully recovered following tenofovir withdrawal[106]. Mitochondrial DNA depletion results in mitochondrial dysfunction in the lamivudine/telbivudine-associated neuromyopathy[107]. During treatment with NUCs, attention should be paid to these adverse events.

FUTURE TREATMENT FOR HBV

Tenofovir alafenamide

Compared with tenofovir, tenofovir alafenamide (GS-7340) is a new tenofovir prodrug, which has demonstrated more potent antiviral activity and lower tenofovir exposures. These might lead to lower nephrotoxicity. Further clinical study will be needed[108-110] (Table 6).

Treatment for HBV cccDNA

In the HBV-infected liver, free HBV DNA and its products are causally related to the activity of liver disease, but the persistence of HBV infection is maintained by the nuclear cccDNA, which serves as a transcription template for HBV mRNA[111,112]. Although there are several opposing views[113], it was reported that HBV cccDNA is noncytolytically degraded by agents that up-regulate apolipoprotein B mRNA editing enzyme and catalytic polypeptide-like (APOBEC) 3A and 3B[23]. In the near future, new therapeutic options to control HBV cccDNA are needed[114-117].

Sodium taurocholate cotransporting polypeptide

Sodium taurocholate cotransporting polypeptide (NTCP) membrane transporter was reported as an HBV entry receptor[118,119]. Iwamoto *et al*[120], Watashi *et al*[121] and Tsukuda *et al*[122] reported that cyclosporine A and its analogs blocked HBV entry through inhibiting the interaction between NTCP and the HBV large surface protein. HBV entry inhibitors might also be useful for controlling HBV infection in the near future.

CONCLUSION

The development of therapies aimed at HBsAg loss, which is the final goal of hepatitis B, is a goal for future research. Further improvements in the therapeutic options for HBV cccDNA are needed.

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P- Reviewer: Devanarayana NM, Frider B, Poovorawan Y, Waisberg J, Zhu F
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