Abstract

Approximately 240 million people globally are chronically infected with hepatitis B virus (HBV), which is an enormous health problem worldwide because it will be developing to chronic liver disease, liver cirrhosis and hepatocellular carcinoma. The primary goal of chronic HBV infection therapy is preventing HBV-related liver injury from moving to end-stage liver diseases. Current therapeutic agents for chronic HBV infection primarily contain pegylated-interferon (IFN)-α and five nucleos/nucleotide analogues (NAs), which include lamivudine, adefovir, entecavir, telbivudine, and tenofovir. In contrast to pegylated-IFN being treated for a finite period of time, NAs are often given for lifelong. However, all of them are not able to entirely eradicate HBV due to the persistent existence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes. Several innovative antiviral agents are currently undergoing clinical trials, which hopefully will be having promising results in the near future. In this review, the following issues will be addressed: (1) Options for chronic hepatitis B therapy; (2) Chronic hepatitis B infection in pregnancy; (3) Predictors of Treatment Response for Pegylated IFN and NAs; (4) Reactivation of CHB infection due to chemotherapy and immunosuppressive therapy; (5) Management of HBV with drug resistance; (6) Management of CHB patients co-infected with HCV or HIV; (7) The role of anti-HBV therapy in HCC prevention; (8) Unknowns in CHB management and future studies of anti-HBV therapy.
Introduction

The definition of chronic hepatitis B (CHB) infection is persistent hepatitis B virus (HBV) infection with the existence of hepatitis B surface antigen in patients' serum lasting for more than six months [1]. Chronicity is common following acute HBV infection in neonates whose mothers are often positive for hepatitis B e antigen (HBeAg) and in young children under the age of 5 years, but unusually occurs when infection is acquired in adulthood [2,3]. The majority of persons with CHB were thought to be infected at birth or in early infancy worldwide [1-3]. The presence of active viral replication and chronic inflammatory liver disease caused by HBV strongly affects the rate of progression to cirrhosis and even hepatocellular carcinoma (HCC). Before the oncoming of antiviral therapy, 5-year survival rate was 55% in patients with HBV-related cirrhosis, compared with 97% in patients with non-cirrhotic liver disease [4].

There are 10 genotypes, from A through J, and numerous subtypes of HBV [5]. Genotype A is the main genotype in northern Europe and the United States. Genotypes B and C are limited to people in eastern Asia and the Far East. Genotype D is found throughout the world but is particularly common in the Mediterranean area, Middle East, and south Asia. Genotype E is indigenous to western sub-Saharan areas, and genotype F prevails in Central America. Other genotypes are relatively not common. Some scattered cases of genotype G have been reported in the United States and France, genotype H in Mexico, genotype I in Vietnam and genotype J in Japan [6,7].

CHB infection is typical of the interaction between the virus, the immune system and the host's liver. This situation leads to wide fluctuations over time all patients' life, resulting in the four phases of CHB infection, which are “immune-tolerant”, “immune-active”, “immune-control”, and “immune reactivation” [8-11].

1. The immune-tolerant phase starts most often in HBsAg-positive children and young adults infected in the perinatal or early childhood period. It’s a continuous process which lasts from perinatal period into young adulthood. Classically, at this stage, serum HBeAg is detectable, HBV DNA levels are high, and alanine aminotransferase (ALT) levels may be normal or only slightly elevated. There is mild hepatic inflammation, gradually developing to fibrosis, and a slim chance of spontaneous HBeAg loss.

2. In an HBeAg-positive immune-active phase, there is active inflammatory disease associated with fluctuating serum ALT levels and gradual decreases in HBV DNA levels. Symptoms of hepatitis may be present and there is more severe, evidenced hepatitis and fibrosis. This stage may last from several weeks to years, and may effectively lead to HBeAg seroconversion.
3. The third phase is the non-replicative or the inactive carrier stage, which is followed by successful HBeAg seroconversion. As soon as HBeAg conversion occurs, serum ALT levels will return to normal with low or undetectable HBV DNA levels. HBeAg seroconversion developing at an early age suggests a good prognosis with a small chance of advancing toward cirrhosis and HCC.

4. The last phase is HBeAg-negative immune reactivation phase. In spite of HBeAg seroconversion, there are still up to 30% of patients who have persistently high ALT and HBV DNA levels, suggesting reversion back to HBeAg-positive with presence of HBV replication and sporadic hepatitis flares. The observations may be attributable to HBV variants with precore or core promoter.

**Options for Chronic Hepatitis B Therapy**

The reason for therapy in chronic HBV patients is to stop progression of chronic liver disease and, moreover, to decrease the risk of cirrhosis and HCC. Antiviral therapies for CHB have been mentioned as guidelines of treatment in several international liver organizations, such as American Association for the Study of Liver Disease (AASLD), European Association for the Study of the Liver (EASL), and the Asian Pacific Association of the Study of the Liver (APASL). Currently the approved therapeutic regimens include pegylated-interferon (IFN)-α and five NAs, which include lamivudine, adefovir, entecavir, telbivudine, and tenofovir (Table 1). Viral suppression can be reached after antiviral treatment in almost 95% of patients [12]. However, the essential drawback of NAs therapy is that it needs long-term use. IFN therapy is of fixed length of time and associates with low response rates and many IFN treatment-related adverse events. NAs appear to have less side effects but have a high chance of developing drug resistance that restricts their long-lasting use. Current anti-viral alternatives on the market might suppress viral replication and improve patients’ survival but they do not get rid of HBV completely, which might be resulting in viral reactivation after stopping treatment. Based on rationale of their use, it’s important to realize that patients as follows are not routinely indicated for instant antiviral therapy: (1) Patients in the immune tolerant stage; (2) Patients in the inactive carrier stage; (3) Patients in the latent HBV infection stage (HBV DNA without HBsAg).
Table 1: Comparison of Antiviral Therapies for Patients with CHB infection.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peginterferon</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Telbivudine</th>
<th>Entecavir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>180 μg weekly</td>
<td>100 mg daily</td>
<td>10 mg daily</td>
<td>600 mg daily</td>
<td>0.5 mg or 1.0 mg daily</td>
<td>300 mg daily</td>
</tr>
<tr>
<td>Pregnancy category</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>B</td>
<td>C</td>
<td>B</td>
</tr>
<tr>
<td>Drug resistance</td>
<td>None</td>
<td>~20% at year 1-70% at year 5</td>
<td>None at year 1-29% at year 5</td>
<td>5% at year 1</td>
<td>25% at year 2</td>
<td>0.2% at year 1</td>
</tr>
<tr>
<td>Side effects</td>
<td>Flu like symptoms</td>
<td>None</td>
<td>None</td>
<td>Myopathy</td>
<td>None</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td>Route</td>
<td>Subcutaneous</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Duration</td>
<td>One year</td>
<td>Lifelong</td>
<td>Lifelong</td>
<td>Lifelong</td>
<td>Lifelong</td>
<td>Lifelong</td>
</tr>
</tbody>
</table>

Lamivudine

Lamivudine, an L-nucleoside analogue, at a daily dose of 100 mg. Long-term therapy with lamivudine in HBV patients with advanced fibrosis or early cirrhosis might deferits clinical progression. However, drug resistance might lead to viral breakthrough after more than six months of lamivudine therapy. The main lamivudine-resistant mutant is located at the YMDD locus in the catalytic domain of the HBV polymerase gene (rtM204I/V ± rtL180M). Recent published results reportedly showed rtA181T/V to be another lamivudine-resistant mutation. Lamivudine resistance has a connection with biochemical and virological breakthrough, which may results in decompensating liver.

Adefovir Dipivoxil

Adefovir dipivoxil is an acyclic adenine nucleotide analogue, which was often used previously; however, because of its limited potency, primary treatment failure (<1 log decline in the serum HBV DNA level at week 12) was observed in 30% of patients. Resistance to this drug was reported in nearly 30% of patients by the end of 5 years of continuous therapy [13]. Adefovir is still used worldwide as initial therapy or every time that lamivudine resistance has emerged. In this scenario, it is often used in combination with lamivudine in patients with advanced disease, because lamivudine is capable of suppressing adefovir-resistant mutants. Adefovir has the drawback of possible nephrotoxicity and should not be used in patients with preexisting damaged renal function.

Entecavir

Entecavir is a nucleoside analog that is more effective than two earlier agents - lamivudine or adefovir. It inhibits multiple functions of HBV DNA polymerase [14]. One study reported that patients treated with entecavir 0.5 mg daily might have undetectable HBV DNA in 83-90% patients, and 24–44 % patients having HBeAg seroconver-
sion after three years of treatment [15]. Entecavir has a much higher genetic barrier to resistance because it needs an extra DNA polymerase mutation in addition to pre-existing lamivudine-resistant mutations. Therefore, rather than a single mutation, multiple mutations are required to cause resistance. In this situation, it could be the most likely that only 2% of treatment-naïve patients have resistance during 5 years of continuous entecavir treatment. Thus, it’s uncommon that treatment-naïve patients develop entecavir resistance. In the long-term follow-up of an international trial on HBeAg-positive and HBeAg-negative patients, the cumulative probability of entecavir resistance was 1.2% after 5 years of entecavir treatment [16]. The benefits of long-term use of entecavir include progressive regression of fibrosis, reversal of the features of cirrhosis, and a decreased incidence of HCC [17,18].

Telbivudine

Telbivudine is a thymidine with an L-configuration of nucleoside analog that has been shown to be more potent than lamivudine. However, there is a strong link between telbivudine and a high rate of resistance. In addition, telbivudine resistant mutations are cross-resistant with lamivudine. Therefore, telbivudine monotherapy is not an eligible therapeutic option of hepatitis B, particularly in lamivudine-resistant patients. Reports in the literature showed that, after 2 years of treatment, genotypic resistance was found in 25% of HBeAg-positive patients and 11% of HBeAg-negative patients, respectively. Thus, telbivudine is not a good choice to be a first-line treatment for HBV infection owing to a high rate of resistance while being treated as monotherapy. Under this circumstance, the drug should not be used if HBV DNA is still detectable after half a year of treatment. Recent studies have reported a significant association between telbivudine use and improvement in renal function in the first year of treatment and were maintained during ensuing years. Most of the improvement was limited to patients with mild renal impairment prior to treatment, and the renal functional improvement was not related to the degree of viral suppression [18].

Tenofovir Disoproxil Fumarate

Tenofovir is a nucleotide analogue, which is structurally similar to adefovir, but it bears significantly more antiviral potency. It was first approved for the treatment of HIV infection. Then it was agreed for treatment of CHB. The overriding concern of tenofovir is its safety, which is not found with entecavir. Although relatively rare in clinical practice, tenofovir therapy has been reported to have not only decreased bone density in HIV-infected patients, but also renal tubular damage in the elderly or persons with preexisting mild renal disease. Amazingly, there has not been resistance to tenofovir after 5 years of treatment in either HBeAg-positive or HBeAg-negative patients. Recent reports in a study have demonstrated that
was significant histologic regression, including reversal of cirrhosis among 74% of patients with pretreatment cirrhosis in a study having more than 300 patients after 240 weeks of tenofovir-based therapy. Patients who previously were considered to be difficult treatment during the time of using resistance-prone antiviral agents, high serum HBV DNA levels (>10^9 copies/mL) were suppressed to undetectable levels in more than 90% of patients during long-term treatment [18,19]. Because of its high genetic barrier to resistance and strong antiviral potency, tenofovir is tend to be used as a standard of care frequently until very recently, especially in cases of previous prolonged exposure to lamivudine with subsequent lamivudine related resistance, or partial response to adefovir. It has been recognized that renal safety and osteomalacia are matters of concern to CHB patients treated with tenofovir. Thus, according to AASLD guidelines, serum creatinine, phosphorus, urine glucose, and urine protein, as well as monitoring of bone mineral density should be assessed before treatment initiation [20].

**Pegylated IFN**

In contrast to IFN, pegylated IFN has more powerful antiviral potency and is clinically tolerated well [21]. Currently, pegylated IFN has been utilized for treating CHB often globally. The standard duration of therapy is 48 weeks. It is important to know to that pegylated IFN treatment is beneficial in patients with baseline ALT values of ranging from 2 to 3 times the upper limit of normal levels, an HBV DNA level less than 10^9 IU/mL, and genotype A or B. There is a concern that IFN is contraindicated in patients with decompensating liver and even cirrhosis because acute hepatitis may develop during pegylated IFN treatment. More recent studies have shown that HBsAg loss might be found in nearly 5% of HBeAg-positive patients within the initial half a year after a complete treatment. This rate compares with rates of disappearance of HBsAg in 5% of patients treated for 96 weeks with entecavir and 3% of those on tenofovir for 48 weeks [22,23]. Even though these differences may be negligible, during long-term follow-up, subsequent responses to pegylated IFN are often related to increasing HBsAg loss, which has not been identified for NAs [24,25]. Compared with NAs, pegylated IFN treatment does not have drug resistance.

**Combined Therapy with NAs and Pegylated IFN**

Theoretically, combined therapy with NAs and pegylated IFN might be able to provide more powerful effect than each of above drug alone and even may achieve the desired effect in a shorter course of NA therapy, which could avoid the risk of drug resistance. However, some data from recent literature suggest that the response of combined therapy was not sustained after stopping treatment [26,27]. Many clinical trials have been undergoing to examine the synergistic effectiveness of combined pegylated IFN with entecavir or tenofovir [28]. Given the
above data, it still merits further study and discussion about this potentially valuable combination treatment to determine whether there is beneficial effect by use of a NAs plus pegylated IFN.

**Chronic Hepatitis B Infection in Pregnancy**

Epidemiologic data suggest that HBeAg-positive mothers who have a serum HBV DNA level more than $10^8$ copies/mL indicate a noticeably risky transmission of HBV from mother to newborn in spite of receiving hepatitis B vaccination within 24 hours of birth [29,30]. Several studies have demonstrated that mothers with higher HBV viral load who receive antiviral therapy with NA in the third trimester might decrease the risk of hepatitis B flares in newborn infants [31]. Many specialists have advocated antiviral therapy starting from the last trimester, starting at 28-32 weeks of gestation in most of the studies, and extending over a period of time after delivery to avoid flares of hepatitis [32]. Telbivudine and tenofovir are classified as category B drugs, whereas lamivudine is classified as a category C drug in HBV-infected women by the FDA [33]. Women who are of child bearing age should be warned not to become pregnant while undergoing treatment with a NA. If pregnancy occurs during treatment, however, the risk of drug withdrawal and subsequent ALT flares must be balanced against the slight uncertainty of harmful effects to the fetus. Because lamivudine has an excellent safety record and the most extensive use during pregnancy, its use can be recommended for highly viremic mothers. Telbivudine, as a category B drug, has been used effectively during pregnancy [31]. Tenofovir is one more practicable option because of both its category B position and its much more powerful than lamivudine or telbivudine. Tenofovir versus control could reduce infant HBsAg seropositivity by 15.8% at 6-12 months' follow-up [34]. Compared with NAs, IFN is contraindicated during pregnancy owing to its adverse effects. It is generally recommended that breast feeding is contraindicated in mothers who continue to receive NA therapy after delivery because a substantial amount of NA tends to move from mothers to newborn babies [34,35]. In spite of the exact safety of lamivudine and tenofovir during breast feeding having not been well examined in women infected with CHB, information from the literature regarding HIV patients advocate the safety of these anti-HBV agents during breast feeding. Given above data, in pregnant women with CHB, NAs therapies using lamivudine, telbivudine, and tenofovir could effectively decrease transmission of HBV from mother to child.
Predictors of Treatment Response for Pegylated IFN and NAs

Predictors of Treatment Response for Pegylated IFN

Usually, HBV DNA level is more likely to reduce quickly in patients with sustained response to pegylated IFN. In clinical practice, using on-treatment serum HBV DNA level as a predictor of therapeutic response is in a conceptually similar way to predictive value of rapid viral response at the first week of chronic hepatitis C treatment so that pegylated IFN treatment can be stopped earlier [36]. Although there has been no broad agreement on the cutoff point of HBV DNA level to predict response, some reports advocated using serum HBV DNA level in a range of week 8 to week 24 to predict sustained virologic response. In addition to HBV DNA level, serum HBsAg level has been becoming an acceptable on-treatment predictor of response to pegylated-IFN therapy. Taken together, HBsAg in combination with HBV DNA predicts the outcome of pegylated-IFN treatment with an absence of decline at week 12 is a good predictor of non-response and to stop therapy. It is advisable that therapy should be continued to 48 weeks if there is any decline at week 24 [37].

Predictors of Treatment Response for NAs

HBV suppression by NAs could greatly benefit from a stronger host immune clearance in terms of lower serum HBV level and higher ALT level given that ALT is greater than 5 times the upper limit of normal level. From a viral kinetics point of view, the more quick suppression of HBV DNA level by an NA, the less risk of drug resistance will be. Because people using long-term NAs treatment run a risk of developing drug resistance, it should be emphasized that prediction of response may need to adjust anti-HBV treatment regimen. In patients who obtained CHB at an early age, HBeAg seroconversion would be lasting longer in pegylated IFN group rather than NAs, which has been generally observed to have a fifty-fifty chance of relapse three years after already HBeAg seroconversion, which, therefore, could not be eligible for a most suitable response marker. HBV will relapse often in HBeAg-positive patients without HBeAg loss and HBeAg-negative patients with premature cessation of treatment despite the fact that NAs could inhibit HBV effectively. A working road map model using HBV DNA as a predictor during treatment has been recommended. In this model, patients with a complete virologic response are suggested to go on treatment with the same drug whereas patients with partial or insufficient therapeutic response may change to more powerful NAs or combine with another add-on NA [38]. Furthermore, guidelines from AASLD, EASL, and APASL supported that the first checkpoint for on-treat-
ment monitoring of HBV DNA levels should be at week 12 after treatment initiation and continue every 12–24 weeks thereafter [20,39,40]. In spite of no current consensus regarding predictive role of HBsAg, Yu et al reported that a low HBsAg level, <3,000 IU/mL at baseline, or HBsAg level, <1,500 IU/mL at week 12, or a rapid on-treatment HBsAg decline of ≥0.5 log10 IU/mL at week 12, may predict higher probability of sustained viral response. However, these cut-off values must be further verified [37,41].

Reactivation of CHB Infection due to Chemotherapy and Immunosuppressive Therapy

Reactivation or flares is a well-acknowledged fatal event and complicated result of CHB patients seeking or undergoing chemotherapy for solid tumors and immunosuppressive therapy for rheumatological diseases, autoimmune disorders, and stem cell or organ transplantation. The main mechanism might be attributable to loss of immune control of the virus during chemotherapeutic or immunosuppressive therapy, which is followed by HBV replication and direct cytolysis of hepatocytes due to severe immune-mediated injury to hepatocytes. The HBV reactivation may be emerged even six months after stopping chemotherapy or immunosuppressive therapy [42,43]. Pragmatically, NA rather than pegylated IFN are generally recommended to be used in CHB patients who are receiving planned immunosuppressive or chemotherapy in terms of safety concerns. NA should be administered until 6 months after cessation of chemotherapy or immunosuppressive therapy. If patients fulfill standard guideline-based anti-HBV treatment instructions, the antiviral treatment might continue until achieving therapeutic endpoints, as suggested by issued standard anti-HBV treatment guidelines. Until very recently, apart from NAs treatment, there is general consensus that prophylactic anti-HBV therapy using hepatitis B immunoglobulins (HBIG) plus NAs is clearly warranted in patients undergoing liver transplantation in order to obtain a protective effect against hepatitis flares, decompensating liver, and even graft loss. As previously stated, an understanding of risk and screening for HBV with the intention of starting appropriate prophylactic therapy has been becoming a fundamental issue in oncologic and immunologic patients. Serological screening markers for HBV might include HBsAg, anti-HBc and anti-HBs. Measurement of HBV DNA is warranted if HBsAg or anti-HBc are positive in case of potential occult HBV infection. However, studies assessing various screening strategies would be justified in terms of cost-effectiveness. Several authors reported that a computerized order entry-based therapeutic control system can provide excellent pre-chemotherapy HBV screening for cancer patients undergoing chemotherapy and can effectively prevent severe acute exacerbation of HBV infection in hospitals among HBV endemic areas [44,45].
Management of HBV with Drug Resistance

Because all NAs share a common target for viral reverse transcriptase (RT), specific mutations in the RT domain therefore leads to resistance after prolonged incomplete suppression of HBV, which is closely linked to treatment failure, hepatitis flare and decompensating liver. Moreover, compensatory mutations might develop at other parts of the polymerase gene afterward, which will improve the replication efficacy of the drug resistant mutant resulting in cross-resistance to another NA. In terms of common HBV drug resistance mutation sites, Rt204 mutation will confer cross-resistance to all L-nucleoside analogs. rtA181V/T is a common mutation pathway between L-nucleoside analogs and acyclic phosphonates. L180M is a compensatory mutation to L-nucleoside analogs. Development of genotypic resistance, as evidenced by detecting mutations in the HBV genome by use of molecular assays, such as sequencing or hybridization, might illustrate HBV drug resistance. HBV breakthrough, 10-fold increase of HBV DNA from baseline level, would begin to emerge eventually during uninterrupted antiviral treatment. It is important to note that patients’ less compliant with drug should be excluded first prior to making a diagnosis of drug resistance. NAs, such as lamivudine and tenofovir, share the same loci of drug resistance mutation at amino acid 204 of the RT, in which lamivudine contains both rtM204I and rtM204V, whereas telbivudine has resistant mutation at rtM204I. Therefore, the treatment planning for lamivudine resistance is similar to telbivudine resistance. NAs, such as adefovir dipivoxil and tenofovir, are the drugs of choice for the treatment of lamivudine-resistant HBV. Among these two drugs, tenofovir has been becoming a better choice rather than adefovir for lamivudine-resistant HBV in terms of its more powerful antiviral effect. Compared to add-on adefovir, direct switching to adefovir from lamivudine confers high rate of subsequent resistance, 18% after one year’s and 25% after two years’ treatment, respectively. Entecavir of daily dose of 1 mg rather than 0.5 mg has a better effect against lamivudine-resistant HBV. Due to potential cross-drug resistance with lamivudine, resistance still occurs in patients using entecavir. As mentioned earlier, rtM204I/V mutation and compensatory mutation rtL180M usually confers lamivudine resistance. Thus, theoretically, previous lamivudine use could decrease the genetic barrier of resistance to entecavir, suggesting a high tendency to treatment failure. Adefovir resistance due to rtN236T could be treated by nucleoside analog and entecavir. Tenofovir exhibits some antiviral effect to adefovir resistance, despite the fact that it shares partial resistance to adefovir. Combined with emtricitabine, tenofovir has better synergistic effect of HBV suppression than tenofovir monotherapy in treating patients with adefovir resistance. Both adefovir and tenofovir have been proved to have effective antiviral activity against entecavir resistant HBV. Adding adefovir to
entecavir would be more reasonable for reducing adefovir resistance and improving antiviral efficacy. Furthermore, switching to or adding tenofovir may have favorable result regarding entecavir resistance [46]. Multi-drug resistance was defined as the presence of genotypic resistance to two or more groups of NAs [47]. Recent report has demonstrated that entecavir-tenofovir combination is an efficient and safe rescue therapy for CHB patients infected with HBV strains resistant to multiple antiviral drugs regardless of the genotypic resistance profiles [48].

Management of CHB Patients with Co-Infected HCV or HIV

HBV and hepatitis C virus (HCV) co-infection is not uncommon in highly endemic areas of CHB infection. Asian patients often acquire HBV infection in very early life. Then they have subsequent HCV super-infection; however, in contrast, European and American patients usually either obtain double infections at the same time or super-infected HBV on chronic HCV infection. Co-infected HBV and HCV patients are more likely to have worsening liver disease and subsequent higher rates of cirrhosis and HCC [49,50]. As a first line therapeutic option of CHB, it is reasonable to suppose that peg-IFN-based therapy could be not only effective in HCV but also in HBV infection. Robust evidence from a largest prospective, randomized, controlled trial using pegylated-IFN and ribavirin therapy in dual HBV and HCV infection reported a high HCV response rate (72% and 83% in genotypes 1 and 2/3 respectively) [51] and HBsAg disappeared 6 months after the end of therapy in 18 (11.2%) of the 161 dually infected patients with a rate of HBsAg seroclearance of 5.4% per year [52]. Currently, no data on newly developing direct-acting antiviral agents on the treatment of combined HBV and HCV infection are available, therefore further large scale, randomized study will be needed.

Epidemiological data suggested an estimated 10% of people worldwide infected with HIV being co-infected with HBV. Because HBV and HIV co-infection speeds up disease progression and results in more severe liver injury, it is increasingly clear that anti-HBV therapy is warranted in combined HBV and HIV infection patients. When highly active antiretroviral therapy (HAART) is needed in treating HBV and HIV co-infection patients, it is prudent to include tenofovir and emtricitabine, which might provide powerful antiviral effect on both HBV and HIV. A meta-analysis showed that tenofovir suppresses HBV to undetectable levels in the majority of HBV and HIV co-infected patients, with the proportion fully suppressed increasing with time on treatment and with little if any virological rebound on treatment [53]. Entecavir, adefovir, telbivudine, and pegylated-IFN are possible alternatives if tenofovir is not available. Otherwise, if HAART is not required agents, antiviral drugs with no activity on HIV, such as adefovir dipivoxil, telbivudine, and pegylated-IFN could be used to treat chronic hepatitis B.
in order to decrease the risk of HIV drug-resistant mutants.

The Role of Anti-HBV Therapy in HCC Prevention

HBV related HCC prevention consists of procedures taken before HCC development because it is a dynamic process from etiologic risk factors to HCC, which actually begin before people realize they are affected. Therefore, HCC prevention relies on preparatory work that can be categorized as primary, secondary, and tertiary prevention. Primary HCC prevention with universal HBV vaccination has become worldwide well-established health policy to protect children against HBV related HCC [54]. To eradicate HBV, which have been recognized to be causally related to HCC, is fundamental to secondary prevention of HCC development. In people already infected with HBV, successful treatment of CHB with either pegylated-IFN or oral NAs can induce regression of fibrosis in some cases, and even reduce the risk of HCC in patients with HBV infection including those with advanced liver fibrosis. Although it does not completely eliminate HCC, treatment with NAs appears to be effective in lowering the risk of HCC in patients with cirrhosis [55]. Antiviral therapies for HBV also play an important role in tertiary prevention of HCC recurrence in patients who had undergone surgical resection for HCC [56]. The purpose of tertiary prevention is to maintain and even maximize the remaining functions of already treated HCC patients in terms of blocking HCC recurrence and progression.

Unknowns in CHB Management and Future Studies of Anti-HBV Therapy

There are many unknowns in management of CHB patients, such as (a) how to treat patients with mildly elevated ALT and low-level HBV DNA (e.g., <20,000 IU/mL for HBeAg positive and <2,000 IU/mL for HBeAg negative); (b) long-term beneficial and adverse effects of anti-HBV therapy of patients in the immune-tolerant phase; (c) lacking of knowledge of optimal duration of consolidation before discontinuation of antiviral therapy in HBeAg-positive persons who seroconverted to anti-Hbe; (d) no data examining optimal duration of therapy before stopping antiviral therapy in HBeAg-negative adults; (e) needing further studies on renal- and bone-related complications after longer NAs treatment. The above questions require randomized, clinical trials to provide answers. There has been no new anti-HBV drug being approved since 2008, when tenofovir was first launched. Being shown to be a potentially valuable drug with potentially reducing clinical dosage and diminishing toxicities, tenofovir alafenamide fumarate (TAF) is newly developing prodrug of tenofovir that enables enhanced delivery of the parent nucleotide and its active diphosphate metabolite into lymphoid cells and hepatocytes. TAF has been undergoing several recent clinical trials. Innovative molecules under
examination include entry inhibitors and short-interfering RNAs (siRNAs), and capsid inhibitors [57-61]. Recent updates on studies targeting ccc DNA are being examined. One study identified two structurally related sulfonamide compounds through a cell-based high throughput screen that blocks conversion of relaxed circular HBV DNA to ccc DNA[62]. In addition to ccc DNA inhibitor, there are several approaches being studies, such as Toll-like receptor agonists [63], immunotherapy (Tarmogen) incorporates multiple HBV antigens to boost CD4+ and CD8+ T cell responses [64].

Conclusions

In this article, we reviewed the available data from the international literature to not only summarize current evidence and advances on strategic management and treatment algorithm of CHB, which is an essential public health issue that has been underestimated worldwide, but also provide a comprehensive description of the recent advances of anti-HBV treatment options and rationale for their use. Thus, attention should be paid to international guidelines, which have been providing general consensus and applicable principles for therapeutic approaches to CHB. Thanks to current first line NAs, the replication of HBV can be suppressed in almost all patients to non-detectable serum HBV DNA levels; however, there is still emergence of HBV resistant mutants in long-term NAs therapy. This is because all the clinically available anti-

HBV drugs share a common target, the viral RT. Thus, judicious adding on potent drug or switching to drug without cross resistance is crucial for effective anti-HBV treatment. Extensive value of data analysis should be used to identify which parameters contribute most to predict therapeutic outcomes. Among these predictors, the roles of on-treatment dynamics of HBsAg and HBV DNA levels have been widely studied and were shown to be potentially valuable tools in early prediction of therapeutic response. Another noteworthy issue would be CHB patients might have existing simultaneously with and usually independently of another medical condition, such as pregnancy, undergoing immunosuppressive or chemotherapy, and co-infecting with HCV or HIV. Those are multifaceted conditions that could be solved in an interdisciplinary approach according to evidence based reports.

Acknowledgement

The authors would like to thank Mrs. Tang for her editorial assistant.
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