Update on HBV Treatment and Management of Antiviral Resistance

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Abstract

Chronic hepatitis B (CHB) is a major public health problem affecting up to 400 million people globally. Complications of CHB including liver failure and hepatocellular carcinoma result in 1.2 million deaths per year, making CHB the 10th leading cause of mortality worldwide. The natural history of CHB is variable and complex. The past decade witnessed important developments for the therapy of hepatitis B and marked the new era of oral therapy. The ultimate goal of CHB therapy is to arrest the progression of liver injury and to prevent the development of liver failure and hepatocellular carcinoma. Currently, six agents are approved for the treatment of CHB. Each of these agents, given as monotherapy, has been shown to produce virological, biochemical and histological benefits for both HBeAg positive and negative CHB. There are, however, limitations in spite of their efficacy. The significant side-effect profile of interferon, for example, limits its long-term use. The approved oral agents are tolerable with prolonged use but drug resistance could limit long-term monotherapy. To date, combination therapy with nucleoside analogue and pegylated interferon or two nucleos(t)ide analogues given for one year does not show superiority in durability of response compared to monotherapy. Ongoing research effort is critical to identify the ideal hepatitis B therapy that is safe, effective and produces durable response with a finite course of therapy. It is equally important to conduct a well designed, prospective natural history study to identify predictors of disease progression. This will accurately guide treatment strategy for this important disease.

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Introduction

Hepatitis B is a major public health problem with an estimate of 300-400 million chronically infected persons globally.[1] Complications of chronic hepatitis B (CHB), including liver failure and hepatocellular carcinoma (HCC), result in 1.2 million deaths per year, making CHB the 10th leading cause of mortality worldwide. HBV is a DNA virus in the family of Hepadnaviridae.[2] There are 8 major genotypes of HBV (genotypes A to H) and their prevalence varies amongst geographic regions. Genotype A is found mainly in North America, Northern Europe, South Asia, and Africa; genotypes B and C are prevalent in Asia; genotype D is more common in Southern Europe, South Asia and the Middle East; genotype E is predominantly found in Africa and genotypes F and H in South and Central America.[3-5]

Chronic hepatitis B (CHB) is defined by the persistence of serum hepatitis B surface antigen (HBsAg) for 6 months or longer.[6] The natural history of CHB is complex and variable. It can be classified into four major clinical phases based on levels of serum ALT, HBV DNA, and HBeAg status.[7] These phases are: 1) Immune tolerance, 2) HBeAg-positive CHB, 3) inactive carrier, and 4) HBeAg-negative CHB. Patients in the immune-tolerance phase tend to have high level of viremia, and persistently normal or near normal serum aminotransferases. In contrast, the anti-HBe-positive inactive carriers typically have lower levels of HBV DNA and normal serum aminotransferases. The emergence of pre-core and basal core promoter (BCP) mutants lead to HBeAg-negative CHB.[8-10] The frequency of these HBV mutants varies worldwide as a result of the different geographic distribution of the HBV genotypes. Patients with HBeAg-negative CHB typically have heterogeneity of disease activities characterized by fluctuating levels of serum aminotransferases and HBV DNA.[11] HBeAg-positive and HBeAg-negative CHB patients with persistent or intermittent elevation of serum aminotransferases and HBV DNA levels, and histological evidence of active hepatitis should be considered for antiviral therapy. The past two decades witnessed important developments for the therapy of hepatitis B. The availability of lamivudine in 1998 marked the new era of oral therapy. It also represents a paradigm shift in the management of this important disease. The focus of this review is to discuss both the advances and the limitations of current treatment of CHB.

Therapy for Chronic Hepatitis B

There are currently seven medications approved for the treatment of CHB by the U.S. Food and Drug Administration (FDA).[6,12] They are peginterferon and standard interferon-

alpha (pegIFN-α, IFN-α), nucleoside (lamivudine, entecavir and telbivudine) and nucleotide (adefovir, tenofovir) analogues. The combination of tenofovir and emtricitabine (Truvada) also has potent activity against HBV, but is only approved for use in the treatment of human immunodeficiency virus (HIV).

The ultimate goal of therapy for CHB is to arrest the progression of liver injury and to prevent the development of liver failure and hepatocellular carcinoma. The most important short- and intermediate-term objective of therapy is to maximize HBV DNA suppression. Long-term studies have provided evidence that spontaneous or treatment-induced HBeAg seroconversion is associated with improved survival for patients with HBeAg-positive CHB.[45,46] HBsAg seroconversion is the most desirable goal of therapy but may require long-term therapy.[13,14] Patients who become HBsAg-negative and develop anti-HBs generally have resolution of liver disease. Complete eradication of the HBV, however, is difficult for it has a tendency to integrate into the host genome or remain latent as cccDNA.[15] A significant reduction in serum HBsAg titer has been observed with antiviral therapy, which correlated with changes in cccDNA, total intracellular HBV DNA and serum HBV DNA.[14] Changes in serum HBsAg titer might be used as a surrogate for liver cccDNA level, especially the latter requiring a liver biopsy.[16]

Each of these agents has been shown to produce virological, biochemical and histological benefit for both HBeAg-positive and negative CHB. The biochemical and histological responses usually parallel HBV DNA suppression. Comparison of the potency of these medications for both HBeAg-positive and HBeAg-negative CHB during the first year of therapy from representative publications is shown in **Table 1**.[7,17-21] Patients with HBeAg-negative CHB tend to have lower baseline serum HBV DNA level compared to HBeAg-positive patients. As a result, there was a higher rate of complete viral suppression for HBeAg-negative CHB with every anti-viral agent. Nucleos(t)ide analogues are more potent in HBV DNA suppression compared to interferon for both HBeAg-positive and HBeAg-negative CHB.

Table 1. Virologic, Biochemical and Histological Response at Week 48-52.

Drug	***Undetectable HBV DNA***		***Normalization of ALT***		***Improvement in Histology***	
	HBeAg+ CHB	HBeAg- CHB	HBeAg+ CHB	HBeAg- CHB	HBeAg+ CHB	HBeAg- CHB
Peginterferon	25%	63%	39%	38%	38%	48%
Lamivudine	39%	72%	66%	74%	59%	63%
Adefovir	21%	51%	48%	72%	53%	64%
Entecavir	67%	90%	68%	78%	72%	70%
Telbivudine	60%	88%	77%	74%	65%	66%
Tenofovir	76%	93%	68%	76%	74%	72%

Interferons. Standard Interferon alfa (IFN-α) was the first drug available for treatment of CHB. In 2005, FDA of the United States approved the long-acting, once weekly PegIFN-α 2a (40 kD branched PEG molecule) for treatment of CHB. PegIFN-α has similar safety profiles and is more effective compared to standard interferon. The recommended regimen for CHB is Pegasys 180 μg subcutaneously weekly for one year. The therapeutic effects of interferon are mainly secondary to its direct antiviral function and immunomodulatory properties. The immunomodulatory effects of interferon can be recognized clinically as flares of hepatitis that often precedes a virological response.[22]

One of the most important treatment end-points for patients with HBeAg-positive CHB is the loss of HBeAg. PegIFNα-2a has the highest HBeAg seroconversion rate (30% at one year) in spite of its lower antiviral potency compared to the nucleos(t)ide analogues. The HBeAg seroconversion rates for the approved oral agents range between 21% and 26% in one year. Long-term follow-up studies of IFN-α therapy from North America and Europe reported that 95%-100% of those who cleared HBeAg continued to be HBeAg-negative after 5 to 10 years of follow-up and 30% to 86% of them eventually lost HBsAg.[13,23] Liver-related complications and mortality were greater in non-responders compared to responders, especially among those with pre-existing cirrhosis.[13] These studies demonstrated that the loss of HBeAg is a reliable treatment end-point that is associated with long-term disease remission. In contrast, long-term follow-up of patients in Asian studies generally showed a lower rate of durable responses to IFN-α, and inconsistent rates of HBeAg and HBsAg clearance.[24-26] These differences noted between the Eastern and Western countries could

reflect differences in viral factors such as genotypes and in the host factors such as the age of disease acquisition.[27,28] There is evidence that patients with HBV genotype A have the highest rate of interferon-induced HBeAg loss compared to the other genotypes. Of note, HBV genotype A is most common in North America and Europe whereas genotype B and C are predominant in Asia.[29-31]

The major disadvantage of interferon therapy is its significant side effect profile that limits its long-term use. It is contraindicated in decompensated cirrhotic and has low efficacy in patients with normal aminotransferases. The therapy for HBeAg-negative CHB is particularly challenging due to its high relapse rate and typically requires prolonged, indefinite course of therapy.[32,33] Despite its limitations, interferon therapy is associated with the highest rates of both HBeAg and HBsAg seroconversion at one year of therapy, underscoring the importance of immunomodulatory properties on viral clearance.

Nucleoside and Nucleotide Analogues. One of the significant impacts of these oral agents is their beneficial effects on end stage liver disease.[34] Unlike interferon, nucleos(t)ide analogues are well tolerated by patients with decompensated liver disease and significant improvement of hepatic synthetic function has been documented.[34] Among the available nucleos(t)ide analogues, entcavir, telbuvudine and tenofovir are most potent in HBV DNA suppression

significantly greater antiviral effect and lower rate of nephrotoxicity compared to adefovir dosed at 10mg.[35-36] Although adefovir at 30mg has higher antiviral potency, it is not recommended for its potential nephrotoxicity, a Fanconi-like syndrome with phosphaturia and proteinuria.[37] Of note, nucleos(t)ide analogues are excreted by the kidneys so dose adjustment is essential in patients with abnormal creatinine clearance.[38]

The rates of HBeAg and HBsAg seroconversion do not correlate to the potency of the antiviral agent. The one-year HBeAg seroconversion rate is similar across the nucleoside and nucleotide analogues (between 21 and 26%) regardless of their antiviral potency.[17-21] Similarly, the one-year HBsAg seroconversion rates are < 1% for all the nucleos(t)ides. For nucleos(t)ides, there is a trend toward increased rates of undetectable HBV DNA with prolonged therapy beyond the first year in the absence of drug-associated resistance. Similarly, the rate of HBeAg seroconversion increased to approximately 30% for lamivudine, adefovir, entecavir and telbivudine at year 2 of continuous therapy for patients with HBeAg-positive CHB.[6,39-42] The durability of HBeAg seroconversion, however, is variable and relapse rates of up to 60% after nucleos(t)ide analogue therapy.[7] HBsAg loss also increases with prolonged monotherapy but at a very low rate. A subset of the patients received continuous therapy with entecavir for 5 years.[43] With the extended therapy with entecavir, an additional 23% (33/141) of patients achieved

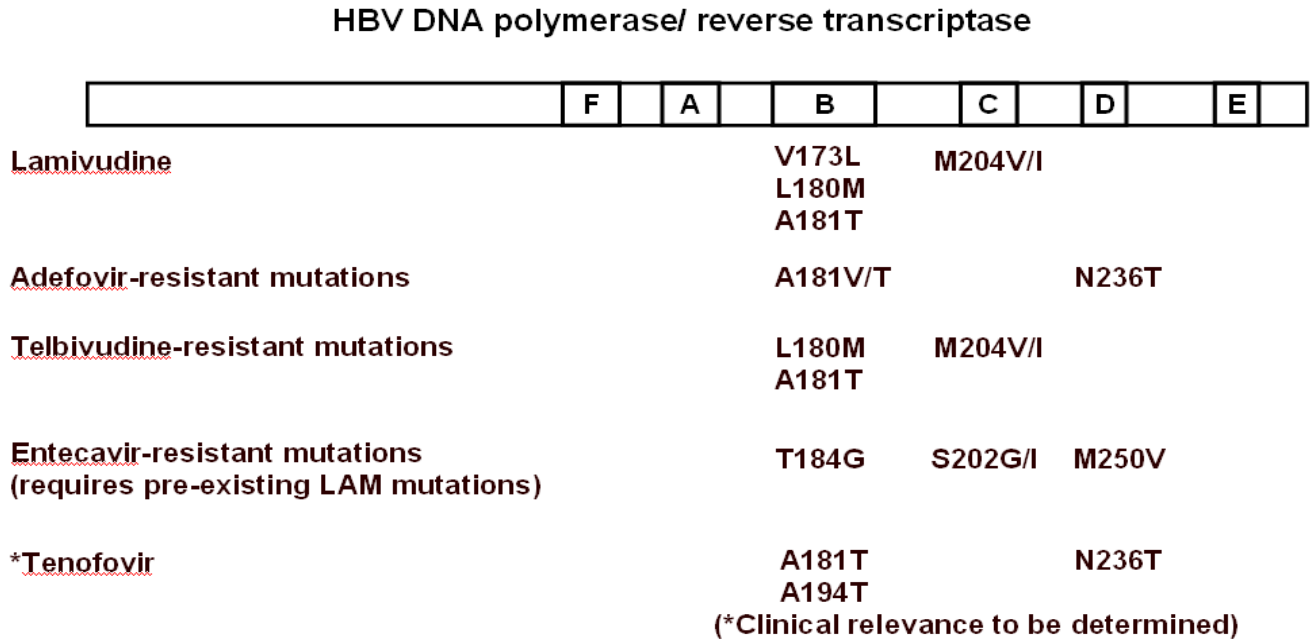

Figure 1. Anti-viral induced mutations at HBV DNA Polymerase/ Reverse Transcriptase. Only the major primary mutations and clinically relevant compensatory mutations are shown.

(**Table 1**). At one year, ≥60% of HBeAg-positive and >85% of HBeAg-negative CHB patients achieved undetectable HBV DNA by RT-PCR assays with these three agents.[18,20,21] Adefovir and tenofovir are both structurally related nucleotides. The clinical dosage of tenofovir 300mg has

HBeAg seroconversion but only 1.4% (2/145) lost HBsAg. Unlike interferon, the nucleos(t)ide analogues are well tolerated even with long-term therapy. The effectiveness and durability of response, unfortunately, could be compromised by the emergence of mutations in the HBV DNA polymerase

which confers to the HBV mutants a selective resistance to the drug. To date, interferon-induced resistance has not been reported and HBV resistance to tenofovir has not been confirmed. The primary site(s) of mutations associated with the nucleos(t)ide antiviral agents are showed in **Figure 1**.[6,44,45]

Drug Resistance and Cross-Resistance.

HBV replicates asymmetrically via reverse transcription of an RNA intermediate. Since its polymerase/ reverse transcriptase (Pol/Rt) lacks proofreading activity, spontaneous mutations are estimated to occur at a rate of one error per 10^4-10^5 nucleotides daily.[46] The resulting random mutations at the polymerase/ reverse transcriptase active site may overlap with the antiviral-induced mutations and facilitate drug resistance.

Antiviral resistance is defined as the selection of HBV mutants conferring reduced susceptibility to a drug that results in primary or secondary treatment failure. While resistance is more likely the cause of secondary treatment failure, it may cause primary treatment failure due to transmission of resistant HBV mutants or due to cross-resistance resulting from previous therapies.[47] The risks of the emergence of drug resistant mutants in the HBV DNA polymerase/ reverse transcriptase increases with duration of therapy, high baseline serum HBV DNA level, incomplete viral suppression during the first 6 months of therapy, noncompliance to therapy and prior exposure to nucleos(t)ide analogues.[6,48] The first clinical manifestation of antiviral resistance is virologic breakthrough that is defined as a >1 $\log_{10}$ increase in serum HBV DNA from nadir in a patient who had an initial virologic response.[47] Drug-resistant mutations can be detected months prior to the rise of the serum HBV DNA. The subsequent biochemical breakthrough with increased serum aminotransferases tends to occur 3 to 6 months after virological breakthrough.[49] Antiviral resistance can be associated with acute hepatitis flare with decompensation of liver disease especially among those with advanced fibrosis.[50] These observations underscore the importance of regular monitoring for early virological breakthrough and adjust antiviral therapy accordingly to prevent biochemical breakthrough.

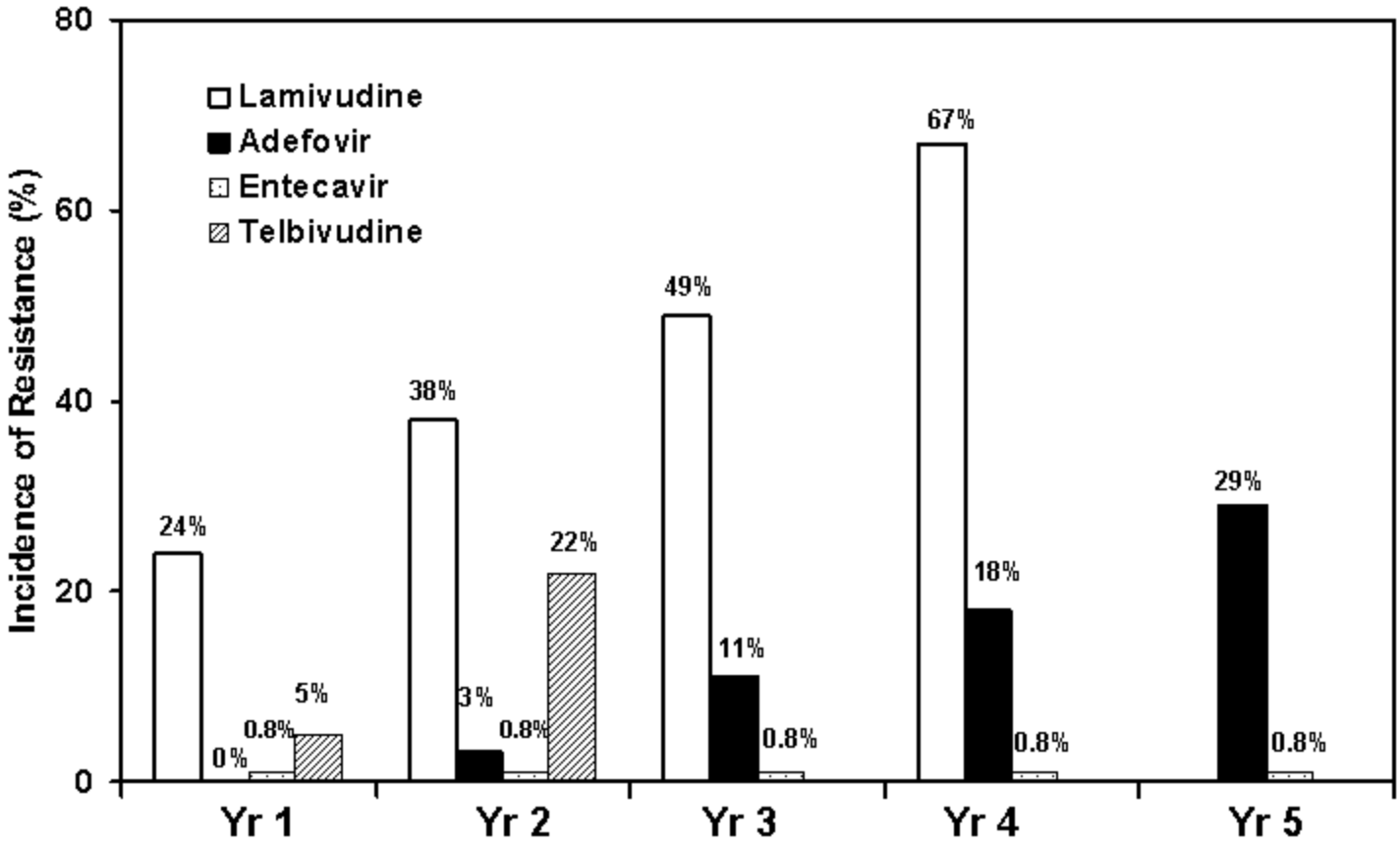

Figure 2. Rate of antiviral resistance with virologic breakthrough on continuous monotherapy.

Lamivudine is associated with the highest rate of resistance, reaching near 70% by year 4 of continuous therapy (**Figure 2**).[7] The primary mutations associated with lamivudine resistance are located in the YMDD catalytic motif of the C domain of the HBV reverse transcriptase (RT) (rtM204V/I) while compensatory mutations (rtV173L, rtL180M) are identified in domain B.[51] By phenotypic analysis, the rtM204V and rtL180M combined mutations induce a 1000-fold decrease of susceptibility to lamivudine in vitro by comparison with wild-type (wt) HBV.[51,52] The main effect of the compensatory mutations is to restore replication fitness of the drug-associated HBV mutant. Thus, HBV DNA level usually increases with continuous therapy after the emergence of the primary mutation.[51,52] Adefovir is generally effective against both wild type HBV and lamivudine resistance mutants.[53] There is evidence to support the 'addition' of adefovir to lamivudine in the presence of lamivudine resistance to prevent the subsequent development of adefovir resistance.[54]

Table 2. Antiviral Resistance, Cross Resistance and Salvage Therapy.

	Antiviral Resistant Mutation						
	Lamivudine-R		**Adefovir-R**		**Entecavir-R**	**Telbivudine-R**	
	M204V/I ±L180M	**A181T**	**N236T**	**A181V/T**	**M204V/I +L180M +T184G or S202I or M250V**	**§M204V/I ±L180M**	**A181T**
***In Vitro* Cross Resistance**	Entecavir Telbivudine	Adefovir Telbivudine	Tenofovir		Lamivudine Telbivudine	Lamivudine Entecavir	Lamivudine Adefovir
Remain sensitive	Adefovir Tenofovir	†Tenofovir Entecavir	Lamivudine Entecavir Telbivudine	†Tenofovir Entecavir	Adefovir Tenofovir	Adefovir Tenofovir	†Tenofovir Entecavir
****Salvage therapy**	Add ADV *or* Add TDF *or* Switch to *Truvada	Add TDF *or* Switch to *Truvada	Add LAM *or* Add ETV *or* Add LdT	Add ETV	Add ADV *or* Add TDF	Add ADV *or* Add TDF *or* Switch to *Truvada	Add TDF *or* Switch to *Truvada

* Truvada are not currently FDA-approved for CHB
****** The suggested salvage therapy is based on both *in vitro* cross resistance profiles and clinical findings. They reflect the experience and opinions of the author
† 1-fold decrease in TDF susceptibility for rtA181V/T *in vitro* (van Bömmel et al, poster #960, AASLD 2007)
§ rtM204V and rtL180M, in addition to rtM204I, have also been associated with telbivudine use
ADV=adefovir, TDF=tenofovir, LAM=lamivudine, ETV=entecavir, LdT=telbivudine

Despite the initial low resistance rate with adefovir, the cumulative resistance rate increased to 29% by year 5 (**Figure 2**).[55,56] The primary site of adefovir-associated resistance mutation, rtN236T, is located in domain D of the HBV reverse transcriptase. This mutation results in a 3- to 6-fold reduction in susceptibility to ADV in vitro and remains susceptible to nucleoside analogues such as lamivudine, telbivudine and entecavir. In contrast, the rtA181V/T mutation of adefovir in domain B was found to have reduced responsiveness to lamivudine and telbivudine in phenotypic assays. It remains susceptible to entecavir and tenofovir (**Table 2**).[51,53,57]

A number of recent studies reported that lamivudine monotherapy can promote the emergence of rtA181T mutation in adefovir treatment naïve patients.[51,58] This single substitution at position rt181 appears to be sufficient to induce cross-resistance between lamivudine and adefovir. In the specific setting of lamivudine resistance with the presence of both rtM204V/I and rtA181T substitutions, the addition of adefovir will not be effective. The addition of tenofovir to lamivudine or switch to Truvada will be the authors' therapy of choice in this case based on the available in vitro data and limited clinical presentations (**Table 2**). These observations with lamivudine and adefovir therapy highlight the important roles of both genotypic and phenotypic assays in identifying the antiviral drug associated mutations and in informing the selection of the subsequent salvage therapy.

The development of entecavir resistance requires pre-existing lamivudine resistance mutations and additional changes in the HBV polymerase/reverse transcriptase: T184 in domain B, S202 in domain C or M250 in domain E (**Figure 1**). The relatively low genotypic resistance rate of entecavir at 1.2% (0.8% associated with virologic breakthrough) in 5 years among previous treatment naïve patients can be explained by a combination of its high genetic barrier requiring multiple mutations to reduce its efficacy, and its anti-viral potency.[61,62] In contrast, the entecavir genotypic resistance rate increased to 51% (43% associated with virologic breakthrough) after 5 years of continuous therapy for patients with pre-existing

lamivudine resistance who were subsequently switched to entecavir.[61] This illustrates the important concept of the emergence of drug resistance in the setting of reduced genetic barrier.

Even though both entecavir and telbivudine have excellent antiviral potency, telbivudine monotherapy is associated with much higher rate of resistance, up to 22% for HBeAg positive CHB at 2 years (**Figure 2**).[18,63] This could be partially explained by the difference in genetic barrier in the development of resistance between the two drugs. Unlike entecavir, telbivudine only requires the single mutation to confer resistance. Cross-resistance between lamivudine and telbivudine is unavoidable since both drugs induce mutations at HBV reverse transcriptase (rt) position 204. Similar to lamivudine, the presence of telbivudine resistance would likely predispose to the emergence of entecavir resistance based on the *in vitro* data.[57,64]

Monitoring and Management of Antiviral Resistance

Antiviral resistance is the major limitation of prolonged nucleos(t)ide analogue therapy. Careful consideration is needed to select first-line therapy in order to avoid the emergence of resistance; especially that may limit future treatment choices due to cross resistance with other agents. Lamivudine, in the authors' opinion, is no longer considered a first-line monotherapy because of its high rate of resistance. Even though the wild type HBV repopulates and becomes the dominant viral species after the discontinuation of antiviral therapy in the setting of resistance, the drug resistant mutants will persist indefinitely in low level. Upon re-challenged with the same drug or drugs with cross resistant profiles, the resistant mutants will have growth advantage and replicate in high level.[49]

HBV DNA quantification is important for initial patient evaluation, for monitoring treatment response and for early detection of virological breakthrough on therapy. The real-time PCR (RT-PCR) quantification assays are reproducible and have a broad dynamic range. RT-PCR assays are, therefore, recommended for HBV DNA baseline determination and monitoring during therapy.[65,66] All patients should have baseline serum HBV DNA, ALT, liver function tests, HBeAg/anti HBe prior to initiating the treatment. Thereafter, serum HBV DNA and ALT should be checked every 3-6 months to ensure adequate response to the treatment and early detection of treatment failure.[47]

For nucleos(t)ide analogue, its antiviral effect is defined as $\geq$ 1 $\log_{10}$ decrease in HBV DNA within 3 months of starting the treatment while its antiviral efficacy is the quantitative $\log_{10}$ reduction in viral load when compared to pre-treatment level.[47] Treatment failure can be primary and secondary. Primary treatment failure is defined as decrease in serum HBV DNA of $\leq$1 $\log_{10}$ IU/mL from baseline after 3 months of starting therapy.[47] Secondary treatment failure is a rebound of serum HBV DNA resulting in an increase of $\geq$ 1 $\log_{10}$ IU/mL in patients with initial antiviral treatment effect.[39,47] This should be confirmed by two consecutive determinations at a 1-month interval. For patients with primary or secondary treatment failure, medication noncompliance should be excluded and if drug resistance is suspected, resistance testing should be performed.[39,47]

Combination Therapy

Nucleoside Analogues and Pegylated Interferon. There are a number of published multicenter clinical trials using a combination of lamivudine and pegylated IFN-α. Lau et al and Marcellin et al reported results of large randomized controlled trials comparing the efficacy and safety of pegIFN-α-2a (180μg weekly), pegIFN-α-2a (180 μg weekly) with lamivudine (100 mg daily) and lamivudine (100 mg daily) alone for 48 weeks in HBeAg positive and negative patients, respectively.[17,30] At 24 weeks of follow-up, the two pegIFN treatment arms (with or without lamivudine) showed the same efficacy in HBV DNA suppression and HBsAg seroconversion, and were superior to that observed with lamivudine alone in both studies. There was a higher rate of lamivudine resistance in the lamivudine monotherapy arm (18%) compared with the pegIFN-α-2a plus lamivudine combination arm (< 1%) at week 48 ($p < 0.001$). It is important to emphasize that in both studies combination therapy was associated with at least a 1 $\log_{10}$ greater HBV DNA suppression at the end of the 48-week treatment period compared to either monotherapy. This finding raises the possibility that with prolonged therapy, the durability of combination therapy will increase.

Combined Nucleoside and Nucelotide Analogues. To date, there has been limited data on the efficacy of combining nucleoside and nucleotide analogues. A study compared the efficacy of adefovir with lamivudine versus lamivudine alone in 115 treatment-naïve, HBeAg-positive predominant patients.[67] The rates of HBeAg seroconversion (20% with monotherapy and 13% with combination) at 2 years were similar. However, there was a significantly lower rate of HBV DNA breakthrough in the combination group (19%) compared to lamivudine monotherapy (44%). Although the combination regimens evaluated so far did not appear to improve efficacy, they did reduce the rates of resistance to nucleoside or nucleotide monotherapy. An optimal combination regimen should work synergistically in viral suppression, increase rates of HBeAg and HBsAg seroconversion, and prevent the occurrence of viral resistance.

Patient Selection for Therapy

Most of the patients with CHB require long-term treatment to suppress the HBV DNA. Prolonged therapy, however, can be associated with increased risk of developing antiviral resistance and potential side effects. In view of the limitations of current therapy, it is important to select patients who are at risk of developing complications from CHB for treatment. The national practice guidelines provided important framework to manage patients with *HBeAg-positive and*

negative CHB.39,68 The summary of the treatment guidelines by the American Association for the Study of Liver Diseases (AASLD) for patients with CHB without cirrhosis is summarized in **Table 3**. Patients with advanced liver disease should be referred to hepatologists for co-management.

Table 3. Summary of AASLD Treatment Guideline for patients with CHB without Cirrhosis.

	HBeAg positive CHB	**HBeAg negative CHB**
***Treat if persistent**	ALT >2 X ULN HBV DNA >20,000IU/ml (10^5copies/mL) - Liver biopsy optional - Immediate treatment if jaundice or decompensated	ALT >2 X ULN HBV DNA >20,000IU/ml (10^5copies/ mL) - Liver biopsy optional - Immediate treatment if jaundice or decompensated
Consider treatment if disease	ALT 1-2 X ULN HBV DNA >20,000IU/ mL (10^5copies/ mL) - Consider liver bx, especially if age >40 yrs, treat if disease on biopsy	ALT 1-2 X ULN HBV DNA 2,000-20,000IU/ mL (10^{4-5}copies/ mL) Consider liver bx, treat if significant hepatic inflammation/fibrosis
Monitor	ALT <1 X ULN - monitor ALT every 3-6 months - monitor HBeAg every 6 months - Consider liver bx if ALT fluctuates, age >40yes, family history of HCC, treat if disease on biopsy	ALT <1 X ULN - monitor ALT every 3 months X3, then every 6 months if stable - HBV DNA ≤2,000IU/ mL (10^4copies/ml) Observe, treat if HBV &ALT increase

* Regardless for the treatment decision, patients should undergo regular hepatocellular carcinoma surveillance according to practice guidelines.

The recommendations on therapy are largely based on serum levels of ALT and HBV DNA. There are, however, continuous debates on the optimal ALT and HBV DNA cut-off values to initiate therapy. For patients who do not meet the clear HBV and ALT criteria for therapy, liver biopsy is essential to determine the degree of hepatic inflammation and fibrosis and to treat if there is evidence of disease. The degree of liver injury and its rate of progression vary significantly among patients with CHB. Factors such as serum ALT, HBV DNA, HBV genotypes, naturally occurring HBV mutants and hepatic steatosis have been implicated in disease progression but their accuracy is imperfect. A better understanding of the natural history and identification of predictors of disease progression are crucial for the selection of patients for therapy.

Although serum ALT levels have traditionally been used as an indicator of the severity of hepatic necroinflammatory activity, emerging data suggest that it does not always reflect the degree of underlying disease in CHB. While the REVEAL Study Group noted that patients with higher baseline ALT levels had increased rates of liver disease progression, more than 80% of the cases of cirrhosis and HCC occurred in patients with ALT activity lower than 45 U/L.[69,70] Other studies have shown that 30-40% of patients with normal serum aminotransferases may have significant degree of liver disease on biopsy.[71] Taken together, these findings suggest that serum ALT activity within the normal laboratory range may not be a reliable prognostic predictor for CHB. Limitations of these studies are the lack of serial ALT measurements during the follow-up period and the lack of detailed patient characterizations. Since serum aminotransferases fluctuate over time, especially among those with HBeAg negative CHB, a single, baseline value cannot be expected to reliably predict the course of a chronic disease. In addition, patients with advanced cirrhosis usually have normal or near-normal ALT. Thus, ALT values must be evaluated in the context of other lab results and clinical features.

The serum concentration of HBV DNA is a measure of the level of viral replication in the liver. Chen et al conducted a long-term observational study on over 3000 HBV carriers in Taiwan for a mean follow-up period of 11 years and found that the risk of cirrhosis and HCC increased significantly proportional to the levels of serum HBV DNA $\geq 10^4$ copies/mL.[69,70] The incidence of cirrhosis increased from 4.5% (relative risk, 1.4) for patients with baseline serum HBV DNA concentrations < 300 copies/ml to 36.2% (relative risk, 9.8) for patients with serum concentrations of $\geq 10^6$ copies/ mL. The relationship between serum HBV DNA concentration and cirrhosis remained independent of HBeAg status and ALT level. Likewise, a high baseline and persistently elevated serum HBV DNA concentration increases the risk of HCC. Of the 164 patients in whom HCC developed, the incidence rates of HCC increased in a dose-response relationship beginning with a baseline serum HBV DNA concentration of $l0^4$ copies/mL. The findings of this study are important, however; it suffers from a number of limitations similar to those of smaller retrospective studies.

The patients in these studies did not have liver biopsies at baseline or during follow-up, so that the subset of patients who developed cirrhosis or HCC within each of the HBV DNA categories could not be assessed as to risk based on histological criteria. For the majority of the cohort, there was no monitoring of serial ALT, HBV DNA levels or HBeAg serology during follow-up. In addition, 85% of this study population had HBeAg-negative CHB. These findings require confirmation before they can be generally applied, especially to young subjects in the immune tolerance phase of the disease.

Naturally history studies collectively provide evidence that high HBV DNA, genotype C, BCP mutation and pre-S deletion are associated with liver disease progression and HCC development in patients with CHB. It is possible that a combination of these viral factors synergistically increases risk for disease complications.

Conclusion

HBV continues to be one a major cause of significant morbidity and mortality despite the availability of effective vaccines and improved therapeutic options. A number of viral and host factors have been implicated in disease progression and development of HCC. However, histological data is lacking in most published studies. Furthermore, viral and host factors may work additively or even synergistically in modifying disease status. The ultimate goal of therapy for CHB is to arrest the progression of liver injury and to prevent the development of hepatic complications such as liver failure and hepatocellular carcinoma. Sustained inhibition of HBV replication has been shown to be associated with normalization of aminotransferases and histological improvement, while HBsAg seroconversion is the best surrogate marker for viral clearance. Choice of first-line therapy taking into account antiviral potency, safety and low risk of antiviral resistance is critical. The ideal hepatitis B therapy should be safe, effective with a finite course of therapy and is associated with sustained and durable response. Ongoing research is essential to evaluate the new and currently available agents, not only as monotherapy, but as combination therapy to identify the synergies necessary to reach the ultimate goal of therapy.

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