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Research Article

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Evaluating Efficacy of Treatment and the Endpoint of Viral Eradication during Chronic Hepatitis B Virus Infection Therapy

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ABSTRACT

Hepatitis B is a viral disease with a high incidence and prevalence worldwide. Hepatitis B can cause acute and chronic liver disease. The clinical presentation ranges from subclinical hepatitis to symptomatic hepatitis and, in rare instances, fulminant hepatitis. Long-term complications of hepatitis B include cirrhosis and hepatocellular carcinoma(HCC). Perinatal or childhood infection is associated with few or no symptoms, but it has a high risk of becoming chronic. A limited number of medications can be used to effectively treat chronic hepatitis B; a safe and effective vaccine is available to prevent hepatitis B infection caused by the hepatitis B virus (HBV). HBV is a double-stranded DNA virus of the Hepadnaviridae family. HBV is a hepatotropic virus that replicates in the liver and causes hepatic dysfunction. HBV is transmitted by percutaneous or permucosal exposure to infectious body fluids, by sexual contact with an infected person, and by perinatal transmission from an infected mother to her infant.

Persons with chronic HBV infection are predisposed to chronic liver disease and have a greater then 200-fold increased risk of hepatocellular carcinoma. Fulminant hepatic failure occurs in approximately 0.1-0.5% of patients and is believed to be caused by massive immune-mediated lysis of infected hepatocytes. A variety of extrahepatic manifestations, including urticarial rashes, arthralgia, and arthritis, are associated with acute clinical and subclinical HBV infection, as well as multiple immune-complex disorders such as Gianotti-Crosti syndrome (papular acrodermatitis), necrotizing vasculitis, and hypocomplementemic glomerulonephritis. HBV is associated with 20% of the cases of membranous nephropathy in children. Essential mixed cryoglobulinemia, pulmonary hemorrhage related to vasculitis, acute pericarditis, polyserositis, and Henoch-Schönlein purpura have been reported in association with HBV infection. Hepatitis B virus (HBV) infection and its sequelae remain a major cause of chronic liver disease worldwide, with nearly 400 million persons infected. Although the majority of individuals with HBV infection will likely remain in an inactive phase associated with low viral replication and histologic remission, a significant proportion will develop chronic hepatitis B.

In conclusion; given the low rate of spontaneous remission as well as the increased risk for progression to cirrhosis and/or the development of hepatocellular carcinoma, there is a continued need for effective therapeutic intervention in chronic hepatitis B.

Keywords- *Chronic Hepatitis B; Fulminant hepatitis; Perinatal; HCC.*

INTRODUCTION

Current treatment guidelines for hepatitis B recommend antiviral therapy only for those with active/advanced liver disease and high serum hepatitis B virus (HBV) DNA levels[1-3] Liver biopsy is an invasive procedure and its accuracy in grading or staging liver disease is limited by sampling error[4], therefore, treatment decision is generally made based on alanine aminotransferase levels (ALT).

Traditionally, persons with ALT values within the normal range were considered to have "healthy" livers. However, several studies found that persons with ALT values that were 0.5-1 times the upper limit of normal had

a higher risk of mortality from liver disease or cirrhosis complications than those with ALT

<0.5 times the upper limit of normal.[5-8] Furthermore, several studies showed that moderate inflammation and/or advanced fibrosis can be found in 28%-37% of patients with chronic HBV infection who had persistently normal ALT.[9-14] These new data have prompted some experts to recommend the abandonment of ALT as a criterion in the determination of candidacy for HBV treatment.[7,8,10-15]

It has also been suggested that the designated upper limits of normal for ALT values in most diagnostic laboratories are erroneously high and the correct upper limit of normal should be 30 U/L for men and 19 U/L for women.[16] Using these lower cut-offs, several studies have found that significant liver disease can be found in 13%–30% of hepatitis B patients with persistently normal ALT.[10,12,14] There are 7 approved therapies for chronic hepatitis B virus (HBV) infection: 2 formulations of interferon (IFN) (standard and pegylated IFN [PEG-IFN]) and 5 nucleoside analogs (NUCs): lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate. Although these therapies are effective

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in suppressing HBV replication, they do not eradicate the virus. Therefore, treatment require a long duration of and sometimes lifelong therapy to derive clinical benefit.

The ultimate goals of treatment for chronic hepatitis B virus (HBV) infection are unquestionable, prevention of the life-limiting outcomes of liver failure and liver cancer. These goals are not, however, practical treatment goals, because liver failure and liver cancer are the results of decades of chronic infection. Rather than rely on these clinical endpoints, HBV treatment trials have relied on surrogate endpoints that reflect viral replication and liver disease activity. Importantly, appropriate surrogate endpoints should be selected based on evidence that they do indeed reflect improvement in clinical outcomes for patients.

Guidelines from professional organizations and recommendations from consensus conferences provide a framework to guide physicians in deciding when to start treatment, which treatment to use, and when to stop treatment.[17-20] Treatment decisions should be made after careful consideration not only of clinical features, hepatitis Be antigen (HBeAg) status, serum HBV-DNA, and alanine aminotransferase (ALT) levels, and liver histology, but also individual circumstances such as family history of HCC, occupational requirements, plans for starting a family (in women), and co-morbid conditions such as those that may preclude the use of IFN or increase the likelihood of adverse events. Other considerations, such as the patient's perceived risk for adverse outcomes, cost and compliance to undergo therapy may influence a decision of both when to start treatment and the choice of therapy (Table 1).

Table 1: Factors to consider in treatment decisions

Factors in disease progression
age
gender
duration of infection
HBeAg status, HBV DNA level
ALT level, histology, clinical portal hypertension, cirrhosis
Factors associated with treatment response
disease activity: ALT level, histology.
HBeAg status, HBV DNA level
HBV genotype (IFN treatment only)
Factors specific to the individual patient
symptoms
age
plans to start a family in women
occupational requirements
family history of HCC
patient›s perception of risk for untreated disease
patient›s perception of treatment response and benefit
cost and healthcare coverage
patient commitment to IFN or oral medications

These studies indicate that hepatitis B patients with persistently normal ALT can have significant liver disease on liver histology and can experience liver-related mortality. However, there are several limitations to these studies. Many studies included small numbers of patients, and persistently normal ALT was often based on two ALT values that were within a few months of each other. The definition of significant liver disease was not standardized and varied from fibrosis only (score of ≥2 on a scale of 0-4) or inflammation only (score of ≥2 on a scale of 0-3 or 0-4) or a combination of inflammation and fibrosis.[21-26] In some studies, only patients with persistently normal ALT and high serum HBV DNA levels were biopsied; therefore, the results cannot be generalized to all patients with normal ALT. Finally, most studies did not report how many patients with persistently normal ALT were not biopsied, raising the possibility of selection bias. Improvement in serum liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and liver histopathological findings, while used in some clinical trials as surrogate endpoints for successful HBV treatment, are not valid endpoints to be used in the clinical setting. The factors that prevent the use of these 2 potential endpoints in the clinic are discussed below. Appropriate surrogate endpoints for hepatitis B treatment include: Suppression of HBV DNA; Hepatitis B e antigen (HBeAg) seroconversion; and Hepatitis B surface antigen (HBsAg) loss.

Table 2: Comparison of Pegylated Interferon and Nucleoside Analogs

Consideration	PEG-IFN	NUCs Analogs
Route of injection	Parenteral, SC injection	Oral
Duration of treatment	1 year	years to lifelong
Antiviral activity	Modest	Modest, Strong, Strongest
Drug resistance	NA	Low, Higher, Highest
Immunomodulatory activity	Yes	No
HBeAg seroconversion (year treatment)	~ 30% > 1year	~ 20% > 1y 40%-50% > 5 years
HBsAg loss (year treatment)	~ 3% > 1 year ~ 10% > 3-5ys	0-3% > 1ys 0-8% > 4-5 ys
Predictors of response	High ALT, low HBV DNA Genotype A (HBeAg+Ve)	High ALT, low HBV DNA
Adverse events	Frequent	Rare
Decompensated liver disease	contraindicated	Indicated
Compensated cirrhosis	Selected cases	Indicated

HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; SC = subcutaneous.

Choosing tuitable drug therapy

Once a decision to initiate treatment is made, the next step is to choose the appropriate drug. The decision regarding whether to use NUC or IFN is based on patient characteristics and patient preferences (Table 2).

Classification of ALT and HBV DNA guide

To determine the correlation between serial ALT and serial HBV DNA levels; at least three ALT values minimum 3 months apart during a 1-year period should be analyzed. ALT patterns that were persistently normal (all values within the normal range), intermittently abnormal (some values within the normal range and at least 1 value above the upper limit of normal) or persistently abnormal (all values above the upper limit of normal). Normal ALT was defined as value of 40 U/L unless specified otherwise; recently proposed new upper limits of 30 U/L for men and 19 U/L for women were used.

HBV DNA patterns were classified into persistently low (all values $<10^5$ copies/mL), fluctuating (some values $<10^5$ copies/mL and at least 1 value $>10^5$ copies/mL) or persistently high (all values $\geq 10^5$ copies/mL). Serum HBV DNA was quantified by hybridization assays with a lower limit of detection of 5 pg/mL (roughly 750 000 copies/mL) prior to January 2000, commercially available polymerase chain reaction assays - Amplicor HBV monitor test (Roche Diagnostics, Indianapolis, IN, USA) with a lower limit of detection of 200–1000 copies/mL between 2000 and 2005, and real-time polymerase chain reaction assays, COBAS TaqMan HBV (Roche Diagnostics) with a lower limit of detection of 29 IU/mL (150 copies/mL) from July 2005 onwards. Baseline HBV DNA tested after January 2000 was classified as <3 $\log^{10}$, 3-5 $\log^{10}$ and >5 $\log^{10}$ copies/mL, and as <5 $\log^{10}$ (undetectable) and >5 $\log^{10}$ (detectable) copies/mL for patients tested before January 2000.

Liver Enzymes and Histopathology Endpoint post therapy

One of the first improvements noted by the clinician after the initiation of antiviral therapy is a reduction in serum ALT and AST. After 1 year of pegylated interferon (PEG-IFN)-based or nucleos(t)ide analog (NUC) therapy, ALT normalization occurs in 34%-51% and 41%-78% of patients, respectively.[27-36] After 5 years, 66%-80% of patients on NUC therapy demonstrate normalization of serum ALT.[37-40] Regardless of the end-of-treatment reduction in ALT level, ALT improvements were not durable. Follow-up studies demonstrate that ALT remained normal in only 32%-60% and 32%-49% of patients 6-12 months after discontinuation of PEG-IFN or NUC therapy, respectively.[27,28,40-42] Reduction in serum ALT is usually among the first laboratory improvements noticed in patients receiving antiviral therapy, preceding complete viral load suppression or serologic conversions. Therefore, stopping therapy based on ALT normalization alone, without consideration of other factors, will usually result in virologic and biochemical rebound.

Another factor abrogating the use of serum ALT as a surrogate endpoint is controversy regarding the definition of normal ALT level. Hepatology experts generally agree that the true upper limit of normal (ULN) ALT for men should be 30 IU/L for men and 19 IU/L for women.[43] Many clinical laboratories will, however, use a ULN level as high as 79 IU/L for men and 49 IU/L for women.[44]

A study of 3233 patients with chronic HBV infection demonstrated that patients with ALT levels 1 or 2 times ULN and even 0.5-1 times ULN experienced more liver complications than those with an ALT level less than 0.5 times ULN.[45] Uncertainty regarding the correct ULN of this biochemical marker renders serum ALT as an endpoint for treatment response not easily applied in the clinic setting.

Improvement in liver histopathology is an attractive surrogate endpoint because it directly measures liver disease activity, and thus should be linked to liver disease outcomes, particularly cirrhosis. Antiviral therapy has been shown not only to prevent progression of liver disease but also to reverse fibrosis.[32] No study has examined the predictive value of this reduction in fibrosis in terms of other virologic and serologic outcomes, or in terms of long-term clinical outcomes. In addition, no study has examined the durability of fibrosis reduction after treatment is discontinued. Given the lack of data and the risks involved with liver biopsy, on-treatment liver biopsy is not a practical means of measuring treatment response.

HBV DNA Level Parameter to Define Treatment Success

The association between serum HBV DNA levels and clinical outcomes of chronic HBV infection was emphasized by data derived from the REVEAL study, a large-scale, long-term prospective study of a population-based cohort of Taiwanese adults with chronic HBV infection. These data demonstrated that both risk for progression to cirrhosis and risk for development of hepatocellular carcinoma (HCC) were associated with elevated serum HBV DNA levels.[46,47]

The effect of treatment-induced reduction in HBV DNA levels on improving clinical outcomes has been examined in patients with advanced liver fibrosis and cirrhosis. In a large randomized trial comparing the efficacy of lamivudine to that of placebo, patients assigned to lamivudine had better clinical outcomes, including reduced rates of progression in Child-Turcotte-Pugh score, variceal hemorrhage, spontaneous bacterial peritonitis, or HCC.[48] Another study demonstrated lower rates of HCC and mortality in patients with cirrhosis who maintained viral suppression on lamivudine and maintained viral suppression, compared with those who had virologic breakthrough.[49]

Clinical endpoints are difficult to measure in the absence of cirrhosis, but virologic response has been shown to be associated with histologic outcome. An analysis of 26 HBV treatment trials found that a 1-log reduction in median serum HBV DNA level corresponded with a 2-point decrease in median histological grading.[50] suggesting that HBV DNA reduction during antiviral therapy is a good surrogate for histological improvement.

While the benefits of suppressing HBV DNA are well supported by these data, the application of this endpoint in clinical practice has not been well defined. PEG-

IFN and NUC agents have been shown effective in suppressing HBV replication, but only a small percentage of patients maintain virologic suppression after treatment is discontinued.[41] Emerging data suggest that the rapidity of viral load suppression once antiviral therapy is initiated may be the most important virologic parameter to guide decisions about treatment endpoints. The globe study comparing telbivudine with lamivudine found that an undetectable HBV DNA level (< 300 copies/mL) at week 24 was associated with an HBeAg seroconversion rate of 41% at 1 year, compared with 4% in those with HBV DNA levels greater than 10,000 copies/mL at 24 weeks.[51] Another study evaluating the predictive value of HBV DNA levels at various points during lamivudine therapy found that HBV DNA levels at week 4 (< 2000 IU/mL) and week 16 (< 800 IU/mL) were the best predictors of a combined endpoint of HBeAg seroconversion, ALT normalization, and absence of lamivudine-resistant mutations after 5 years of treatment.[52] Viral kinetics also proved important during treatment with PEG-IFN.

In a study of 66 patients receiving PEG-IFN and lamivudine, HBV DNA suppression at week 8 was a predictor of sustained virologic response, defined as loss of HBeAg, anti-HBe seroconversion, and HBV DNA < 10,000 copies/mL at 1 year.[53] In contrast, patients without early virologic response were highly unlikely to experience a sustained virologic response, with a negative predictive value of 92%.

These data support the use of HBV DNA levels to make clinical decisions for patients with chronic HBV infection on antiviral therapy. For patients with cirrhosis or advanced fibrosis, antiviral treatment is lifelong, as the benefit of continued virologic suppression outweighs the risk for virologic rebound and biochemical flare if treatment is withdrawn. For these patients, the treatment endpoint is complete virologic suppression (generally defined as < 60 IU/mL).[54] but treatment is never discontinued unless viral resistance develops or the patient is unable to tolerate medication.

Durability of response in patients who achieve HBeAg loss and decrease in HBsAg Levels

HBeAg seroconversion remains a valid clinical endpoint in patients who are positive for HBeAg. In an early study of IFN-alpha, survival until liver transplantation or death and lack of clinical complications was significantly better in treated patients who cleared HBeAg than in patients who did not (P = .004 for survival and P = .018 for absence of clinical complications).[55] This finding has been confirmed by other studie.[56] It is, however, important to emphasize to patients that seroconversion can take years to occur, and it does not occur in all patients. Seroconversion occurs at a rate of approximately 20% of patients per year of antiviral therapy and increases over time.[57]

The validity of HBeAg seroconversion as a treatment endpoint has been questioned, because low levels of HBV DNA persist even after HBeAg seroconversion. Furthermore, HBeAg reversion may occur. In one study, 24% of patients developed HBeAg-negative hepatitis with detectable HBV DNA, and 4.1% developed HBeAg reversion after first experiencing HBeAg seroconversion.[58]

Conversely, 92% of study patients who achieved HBeAg seroconversion during lamivudine treatment maintained seroconversion after 5 years. Patients had completed at least 12 months of lamivudine after seroconversion.[59,60] Similar results have been reported with entecavir, telbivudine, and PEG-IFN.[61-63]

HBeAg remains a worthy therapeutic endpoint because of its association with improved clinical endpoints. Most experts recommend treatment of at least 6 months and preferably 12 months after seroconversion with an NUC. After treatment discontinuation, reappearance of low-level HBV DNA almost always occurs. The threshold at which this low-level HBV DNA becomes concerning is not known, although most providers would consider reinstituting antiviral therapy if the HBV DNA level rises above 2000 IU/mL, or if HBeAg reversion occurs.

HBsAg loss has long been the desired endpoint of treatment for chronic HBV infection. Prospective studies of patients with chronic HBV infection have reported lower rates of all adverse liver outcomes in patients who lost HBsAg spontaneously, compared with those who did not.[64,65] A study of 218 patients who were followed for a mean of 63 months after spontaneous HBsAg clearance found that none of the patients who were cirrhosis free and HBV monoinfected at the time of HBsAg loss developed cirrhosis or HCC during follow-up.[64]

In contrast, the incidence of cirrhosis and HCC was 3.4% and 0.7%, respectively, in those who remained HBsAg positive.

Unfortunately, the rate of HBsAg loss with available HBV treatments is low. For patients undergoing NUC therapy, HBsAg loss has been reported to occur in 0%-2% of HBeAg-positive patients and in less than 1% of patients who are HBeAg negative at the end of 1 year. After 3-5 years of treatment, 2%-8% of HBeAg-positive patients have been reported to have developed HBsAg loss, but the rates in HBeAg-negative patients continue to be discouragingly low (0%-5%).[27-39]

The low rate of HBsAg loss with currently available therapies renders this an impractical endpoint. However, as data emerge and use of new assays increases, decline of quantitative HBsAg levels may become more widely used as a means to guide therapy.

CONCLUSION

Decisions regarding when to start treatment, which therapies to use, and when to stop treatment must take into consideration not only viral or disease factors, but also individual patient circumstances and preferences to achieve optimal results.

Because the mechanism of action of NUC therapy is to inhibit the reverse transcription of the pregenomic HBV RNA to HBV DNA, these drugs have no effect on the covalently closed circular DNA reservoir within infected hepatocytes. Therefore, the endpoint of viral eradication is not feasible with these drugs.

Hepatitis B with cirrhosis, the endpoint of therapy is prevention of clinical complications, including liver

cancer and hepatic decompensation; the treatment is generally considered lifelong.

Hepatitis B without cirrhosis, clinical sequelae take decades to occur, so that the use of surrogate endpoints is necessary to guide treatment for chronic HBV infection.

Chronic HBV infection and HBeAg positive, HBeAg seroconversion remains a valid endpoint, and the standard of care is to discontinue treatment 6-12 months after hepatitis B seroconversion is achieved. The development of HBeAg-negative chronic hepatitis B, or HBeAg reversion must be monitored.

HBeAg-negative chronic hepatitis B, the only clear endpoint is HBsAg seroconversion. Because this endpoint occurs so rarely, many consider the treatment of HBeAg-negative chronic hepatitis B to be lifelong. As further data emerge, the use of viral kinetics or quantitative HBsAg titers to guide duration of therapy may become possible in this challenging issues.

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