Management of Initial HBV Therapy for an HBeAg-Negative Patient: A Case Discussion

Calvin Pan, MD, Ke-Qin Hu, MD

Abstract

A case study of a 45-year-old Chinese woman with chronic hepatitis B (CHB) diagnosed in 1999 …...
[N A J Med Sci. 2011;4(1):50-56.]

Key Words: *Chronic Hepatitis B, Antiviral Therapy, Treatment Monitoring.*

History

This is a 45-year-old Chinese woman with chronic hepatitis B (CHB) which was diagnosed in 1999 during her first pregnancy. She was referred to the GI clinic for further evaluation. The patient was born in China with 3 healthy children, and moved to the United States 20 years ago. She wanted to know if she could be treated for CHB.

Current Presentation

Baseline laboratory evaluations reveal the following:

- Hepatitis B surface antigen (HBsAg): positive
- Hepatitis B e antigen (HBeAg): negative
- HBV DNA: 1,650,000 IU/mL
- Alanine aminotransferase (ALT): 96 IU/L [Lab refference NL $\leq$40 IU/L]
- International normalized ratio: 1.0
- Total bilirubin: 1.1 mg/dL
- Albumin: 3.9 mg/dL
- HBV genotype: D

Calvin Pan, MD
Division of Liver Diseases
Department of Medicine, Mount Sinai Medical Center
Mount Sinai School of Medicine, New York, NY
Ke-Qin Hu, MD
Division of Gastroenterology and Hepatology
University of California
Irvine, School of Medicine, Irvine, CA

(Corresponding Author)
Calvin Pan, MD
Division of Liver Diseases
Mount Sinai Medical Center
Mount Sinai School of Medicine
132-21 Forty First Avenue,
Flushing, NY 11355
Tel: 718-888-7728 Fax: 718-888-7738
Email: cpan100@gmail.com

You ordered a liver biopsy and the results indicate moderate inflammatory activity (grade 2) and fibrosis (METAVIR) stage 3-4. Based on her HBV DNA level, elevated ALT (ULN = 19 IU/L) and the liver biopsy findings, you explain to the patient that she meets the criteria for initiating HBV treatment as recommended by current guidelines. She agrees to begin the treatment and you discuss with her on the options of HBV treatment.

Question A:
What type/duration of regimen would you recommend to this patient for initial HBV therapy?
A. Nucleos(t)ide analogue monotherapy for an indefinite duration
B. Combination nucleos(t)ide analogue therapy for an indefinite duration
C. Peginterferon alfa-2a for 48 weeks

Answer analysis. Answer (A) is the best choice because several clinical trials have demonstrated that nucleos(t)ide analogue monotherapy is associated with high rates of HBV DNA suppression and ALT normalization in HBeAg-negative patients. This patient also has significant fibrosis, which might increase the risk of worsening liver function during Interferon treatment.

Answer (B) is suboptimal because there is currently no evidence that combination of antiviral therapy has improved efficacy compared with monotherapy using potent agents which have a high barrier to resistance in treatment-naive patients. Current guidelines do not recommend combination treatment as the first-line therapy.

Answer (C) is probably not the best choice for this patient due to the lower rate of response to peginterferon alfa-2 in patients infected with HBV genotype D vs. genotypes A, B, and C. In addition, lower response rates have been reported in patients with high baseline HBV DNA levels. Treatment with peginterferon alfa-2a is also associated with a higher incidence of side effects compared to nucleos(t)ide analogue therapy. If the patient were younger and considering a future pregnancy, this option might have had more in its favor.

You discuss all the available treatment options with the patient, including your recommendation that nucleos(t)ide monotherapy is the best option for her. The patient accepts your recommendation to start therapy with nucleos(t)ide analogue monotherapy. You now must decide which oral nucleos(t)ide would provide the highest likelihood of treatment success. You discuss the advantages and disadvantages of each option with the patient.

Question B

Which nucleos(t)ide monotherapy would you recommend?
A. Telbivudine
B. Entecavir or tenofovir
C. Adefovir or lamivudine

Answer analysis. Answer (B) is the optimal choice, based on the most recent guidelines. The selection of either entecavir or tenofovir is likely to achieve rapid and substantial reductions in HBV DNA levels with lowest drug resistance rates (< 1%) in treatment-naive patients among nucleos(t)ide analogues approved for the treatment of HBV.

Answer (A) is suboptimal because despite achieving high rates of HBV DNA suppression in the short term, telbivudine has a lower genetic barrier to resistance and higher cumulative resistance rate relative to those observed with entecavir or tenofovir in separate studies.

Answer (C) is suboptimal because of the lower potency and low genetic barrier to resistance associated with both lamivudine and adefovir over a 4-5 year period relative to other available agents in pivotal comparative studies (eg, entecavir vs lamivudine and tenofovir vs adefovir).

You have decided to treat the patient with either entecavir or tenofovir monotherapy. In the absence of previous HBV therapy and genotypic resistance, there are few factors that may drive selection between entecavir and tenofovir as first-line therapies. Insurance coverage, some tolerability concerns in special populations and product information regarding dosing requirements should be taken into consideration when making your selection for each individual patient.

After inquiring about the patient's daily routine and work schedule, she expresses concern that she might find it difficult to observe the recommendation in the product information that entecavir should be taken on an empty stomach because she tends to eat frequent small meals throughout the day at her corner store. As a result, she choose the therapy with tenofovir.

In preparation for this you assess her renal function by measuring serum creatinine and calculating the estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) equation and find that her eGFR is 62 mL/min which does not require tenofovir dosing adjustment. However, her eGFR needs to be monitored closely. The patient is then initiated on tenofovir 300 mg/day every 24 hours with no food restrictions

Question C:

When should the patient come in next for clinical and laboratory assessment?
A. Week 24 of therapy
B. Week 12 of therapy
C. Week 4 of therapy

Answer analysis.

Answer (B) is the optimal choice based on the recommendations from the AASLD guidelines for on-treatment monitoring during nucleos(t)ide analogue therapy in patients with chronic HBV infection.

Answer (A) is suboptimal because waiting until Week 24 for initial monitoring will not allow for the identification of primary treatment nonresponse or for prompt identification of nonadherent patients and initiation of adherence counseling if necessary.

Answer (C) is suboptimal because, although HBV DNA response at Week 4 has been found to be predictive of long-term lamivudine treatment durability, there are no data to suggest that there is a similar association with Week 4 HBV DNA suppression with the newer, potent nucleos(t)ides that have high barriers to resistance, such as entecavir and tenofovir.

HBV Treatment Outcome

You ask the patient to return for a follow-up visit at Week 12 to determine renal function and HBV DNA level. The patient achieves a > 2 $\log_{10}$ decrease in serum HBV DNA at Week 12. Her HBV DNA level is undetectable at 24 and 48 weeks and her renal function remains steady in the 60-70 mL/min range throughout, so you continue tenofovir therapy indefinitely and arrange to conduct follow-up assessments on DNA every 12 months, serology every 6 months and renal function every three months.

Discussion

This case focuses on the most important factors to consider when selecting a frontline treatment regimen in the setting of HBeAg-negative chronic HBV infection and emphasizes optimal strategies for on-treatment management. The patient is a middle-aged woman of Taiwanese decent who presented with an HBV DNA level of 650,000 IU/mL, an ALT of 50 IU/L, and moderate liver fibrosis. Based on several of the most recently updated guidelines, she met the criteria for treatment candidacy in HBeAg-negative patients because she had an HBV DNA level ≥ 20,000 IU/mL and moderate fibrosis on liver biopsy. In addition, her ALT level was substantially above the upper limit of normal (most recently defined by the AASLD as 19 IU/L in women).

The first decision point in this case involved the choice of initiating therapy with peginterferon alfa-2a, nucleos(t)ide analogue monotherapy, or nucleos(t)ide analogue combination therapy. Starting treatment with a single potent nucleos(t)ide analogue was the most appropriate choice based on the results of several clinical trials showing that nucleos(t)ide analogue monotherapy is associated with high rates of HBV DNA suppression and ALT normalization in HBeAg-negative patients regardless of genotype. The durability of virologic response in most patients with HBeAg-negative chronic HBV infection is dependent upon continued therapy and the efficacy, safety and tolerability of nucleos(t)ide analogues used for long-term treatment. Peginterferon alfa-2a therapy for the standard 48 weeks was not considered the optimal choice for this patient due to the low rate of sustained virologic response in high baseline viral load, genotype D infections following a finite treatment period of this duration in patients with HBeAg-negative

chronic HBV infection. The duration of peginterferon alfa-2a therapy is generally limited by the higher incidence and greater severity of toxicities relative to nucleos(t)ide analogue therapy and is not indicated for more than 48 weeks' duration for chronic HBV infection. However, some studies lately suggested prolong peginterferon treatment to 72 weeks was better than 48 weeks in achieving more durable clinical outcomes in HBeAg negative patients. Nucleos(t)ide analogue combination therapy was also a suboptimal choice because currently there is no evidence that combination therapy with the most potent and durable nucleos(t)ides has any advantage over monotherapy in first-line therapy. Ongoing studies may provide more data on this approach, but the potential benefits with regard to both efficacy and resistance remain theoretical at this time.

It is recommended that renal function be assessed before initiating tenofovir therapy in patients. Meassurement of serum creatinine can calculate estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) equation which accounts for 4 variables: age, serum creatinine, gender and ethnicity. Creatinine clearance is Another accurate method is to calculate the creatinine clearance with Cockcroft –Gault equation but requires a timed 24 hours urine collection and has limited use in in children, severe renal impairment; age over 85, and body mass significantly outside the normal range.

The next challenge presented by this case was the selection of the first-line nucleos(t)ide analogue therapy. There are currently 5 nucleos(t)ide analogues approved for the treatment of chronic HBV infection: adefovir, entecavir, lamivudine, telbivudine, and tenofovir. However, the most recent guidelines generally recommend the most potent and durable agents approved at the time of the guideline publication. The preference for entecavir or tenofovir over adefovir, lamivudine, and telbivudine is based on greater virologic efficacy and/or better resistance profiles, which impart improved long-term therapy durability. Entecavir and tenofovir have both been associated with significantly higher rates of virologic suppression in randomized studies comparing each agent with lamivudine and adefovir, respectively, and extremely low rates of resistance after prolonged therapy (1.2% at 6 years and 0% at 2 years, respectively). Although telbivudine has also been shown to be associated with high rates of virologic efficacy, its genetic barrier to resistance is lower than those of entecavir and tenofovir resulting in a higher cumulative resistance rate from 2 years onward. Resistance is a particularly important concern for HBeAg-negative patients due to the likelihood that they will require indefinite therapy in order to sustain virologic response. Adefovir is not recommended by the society guidelines (EASL and AASLD) due to its suboptimal potency and lower relative barrier to resistance compared with tenofovir[1,2]. Lamivudine is no longer recommended as a frontline agent due to its low barrier to genetic resistance, resulting in a high rate of resistance that increases with prolonged use. Either entecavir or tenofovir would be

expected to provide rapid and durable HBV suppression in this case so any lesser everyday factors may push the decision toward one agent or another. However, in this case where healthcare coverage limitations were not an issue, the patient's work and life schedule tipped the selection of first-line agent in favor of tenofovir, because entecavir is recommended to be taken on an empty stomach at least 2 hours after a meal and 2 hours before the next meal. If the patient's GFR were lower than 50, taking entecavir could have the option of daily dosing in liquid form instead of taking it less frequent.

The final management decision highlighted the importance of regular and timely on-treatment monitoring, regardless of the nucleos(t)ide used. For less potent agents, assessment at Week 12 can assist in identifying suboptimal responses and virologic breakthrough, allowing for preemptive changes in the regimen to avoid the development of resistance. With the more potent and durable agents where suboptimal response and genotypic resistance are much less likely, the predominant guidelines recommend the same monitoring schedule to allow the identification of patients with primary nonresponse which is commonly associated with nonadherence, thereby facilitating the implementation of adherence enhancement measures. In addition, the AASLD guidelines recommend on-treatment monitoring during nucleos(t)ide analogue therapy in patients with chronic HBV infection of HBV DNA levels at 12- to 24-week intervals following the initial visit and HBsAg levels every 24-48 weeks. In regimens utilizing tenofovir, specific monitoring frequency has not been defined in patients without renal impairment. However it is recommended that for tenofovir treated patients, routine monitoring of calculated creatinine clearance and serum phosphorus may be performed in patients with mild renal impairment[2]. The prescribing information of adefovir, another nucleotide, states monitoring of serum creatinine every 3 months is necessary for patients with medical conditions that predispose to renal insufficiency and in all patients on adefovir for more than 1 year. More frequent monitoring should be performed in patients with pre-existing renal insufficiency due to the potential, albeit rare, for renal toxicity. It is prudent to follow these same directions for tenofovir until further direction is available.

Goals of HBV Therapy and Updates on Approved Therapies

The current goal of HBV treatment is the prevention or reversal of complications and death resulting from advanced liver disease, which is characterized by unchecked viral replication and immune system-mediated hepatic damage.[1,2,3] HBsAg loss and seroconversion to anti-HBs is associated with complete and definitive remission of the activity of chronic HBV infection and an improved long-term outcome; however, this is not an achievable goal for most patients. As a result, treatment for HBeAg-negative chronic HBV infection is designed to achieve durable suppression of HBV DNA to levels below the limit of detection by PCR-based assays because several studies have demonstrated a strong

correlation between ongoing HBV replication and disease progression.[4,5,6]

The treatment of HBeAg-negative chronic HBV infection presents a particular challenge for clinicians because HBeAg-negative patients are generally in a late phase of infection that is associated with progressive liver disease and poorer prognosis relative to HBeAg-positive patients.[7] The 2 main avenues for initial treatment of HBeAg-negative chronic HBV infection include interferon (IFN) therapy (interferon alfa-2b or peginterferon alfa-2a) or nucleos(t)ide analogue therapy. Currently 5 nucleos(t)ide analogues are approved for use in chronic HBV infection: adefovir, entecavir, lamivudine, telbivudine, and tenofovir. Among the approved therapies, the most recent treatment guidelines recommend peginterferon alfa-2a, entecavir, or tenofovir as preferred frontline antiviral agents.[1,3]

Selection of Peginterferon alfa-2a vs Nucleos(t)ides as First-Line Therapy

The clinician must decide between the available options for first-line therapy based on the specific circumstances of each patient. The main factors that drive the initial treatment decision between a peginterferon alfa-2a regimen or an approved nucleos(t)ide analogue include efficacy (and durability of response), tolerability, risk of resistance, duration of treatment, and mode of administration.[2]

One of the fundamental differences between the 2 antiviral treatment modalities relates to their specific duration; peginterferon alfa-2a therapy is restricted to a limited duration (typically 48 weeks) whereas nucleos(t)ide analogue therapy can be, and often is, prolonged over long or indefinite time periods in HBeAg-negative patients. Although nucleos(t)ide analogues are generally well tolerated and have the considerable advantage of oral administration vs. injection required by peginterferon alfa-2a, one disadvantage of long-term therapy with these agents is the potential for the development of drug resistance that can reduce the benefits of therapy and compromise patient outcomes.[8]

Peginterferon alfa-2a ± lamivudine has been demonstrated to be superior to lamivudine in achieving HBsAg, virologic, and biochemical responses when each was administered for a finite duration of 48 weeks in 537 HBeAg-negative patients.[9] However, the incidence of adverse events was significantly lower among patients treated with lamivudine alone ($P < 0.001$). Long-term observational study of these patients found that the benefits associated with peginterferon alfa-2a ± lamivudine were sustained and HBsAg clearance continued to increase after treatment discontinuation.[10,11] HBV genotype has been found to strongly correlate with SVR to interferon in both HBeAg-positive and HBeAg-negative hepatitis.[12,13] A pooled retrospective multivariate analysis conducted by Erhardt and colleagues demonstrated that HBV genotype D (vs. A, B, or C), elevated ALT, and HBeAg-negativity were each associated with a significantly reduced rate of sustained virologic response to interferon-based treatment among 1229 HBeAg-positive and HBeAg-negative patients.[13] The lowest rates of SVR with interferon alfa-2b have been shown to occur in HBeAg-negative patients infected with genotype D and high viral load.

The critical endpoint of HBsAg clearance occurs more frequently (10% to 12%) in HBeAg-negative patients treated with peginterferon alfa-2a therapy for 48 weeks than patients treated with nucleos(t)ides for the same period of time.[11] Increasing evidence suggests that HBsAg kinetics at early points in therapy are predictive of long-term treatment success in HBeAg-negative patients receiving peginterferon alfa-2a with or without lamivudine.[14,15] Recent trials have shown that when undetectable HBV DNA is sustained, rates of HBsAg loss continue to increase over 2-6 years of treatment with newer nucleos(t)ide agents, suggesting that rates comparable to those achieved with 48 weeks of peginterferon alfa-2a may be achieved at some future time point.[16-20]

Factors in Selecting an Oral Nucleos(t)ide Analogue-Based Regimen for Initial Therapy

Among the 5 nucleos(t)ide analogues approved for the treatment of chronic HBV infection, only entecavir and tenofovir are the recommended agents for initial therapy in HBeAg-negative patients, according to the most recent treatment guidelines published after both agents were commercially available.[1,3] Both agents are also approved lately by FDA to treat HBV patients with decompensated liver diseases. Although head-to-head randomized comparative studies of the more potent agents have not been performed, these recommendations are based on the results of several clinical trials demonstrating higher virologic efficacy and/or better resistance profiles with these agents relative to lamivudine or adefovir. Specifically, entecavir suppressed HBV DNA to undetectable levels by Year 1 in 90% of treatment naïve HBeAg-negative patients vs. 72% of patients receiving lamivudine ($P < 0.001$).[16] Treatment of HBeAg-negative patients with tenofovir resulted in undetectable HBV DNA in 93% at Year 1 vs. 63% in adefovir recipients ($P < 0.001$).[18] Telbivudine use has also been associated with very high levels of virologic response with 88% of HBeAg-negative patients achieving undetectable HBV DNA after 1 year of treatment vs. 71% of lamivudine treated patients ($P < 0.001$).[22] However, it is not a recommended first-line regimen in current guidelines due to high cumulative resistance rates.[1,2]

Selection of a nucleos(t)ide agent should also take into account any baseline factors that might impact the likelihood of treatment response. In patients treated with nucleos(t)ides there are conflicting reports of an association of high baseline serum ALT levels (> 3 x ULN) and high activity scores on liver biopsy ($\geq$ A2) with increased likelihood of virologic response.[23] Low baseline HBV DNA level ($< 2 \times 10^4$ IU/mL) has been identified as a more consistent predictor of virologic response for agents such as lamivudine, adefovir and telbivudine.[1] It has been suggested that for the more potent

nucleos(t)ide analogues, baseline HBV DNA does not effectively predict the likelihood of achieving and maintaining undetectable HBV DNA however conflicting reports on this association have been made regarding entecavir treatment.[24] Finally, HBV genotype does not appear to influence the response to any nucleos(t)ide analogues.[1]

Considerable interest exists in identifying on-treatment predictors of treatment response. The best on-treatment predictor of sustained response to lamivudine, adefovir, or telbivudine is a virologic response at 24 or 48 weeks (undetectable HBV DNA using a real-time PCR assay), which has been associated with a lower incidence of resistance, an improved chance of maintained virologic response, and a higher frequency of HBeAg seroconversion in HBeAg-positive patients.[25,26] In another study of 74 patients with HBeAg-positive chronic HBV infection treated with lamivudine, achieving HBV DNA < 2000 IU/mL at Week 4 and < 800 IU/mL at Week 16 significantly predicted positive Year 5 outcomes, including HBV DNA < 400 IU/mL, normalized ALT, HBeAg seroconversion, and the absence of resistance.[26]

Other factors that may influence the choice among the 5 available oral nucleos(t)ide analogues include pregnancy (or potential pregnancy), presence of coinfections and/or comorbidities, schedule/food restrictions, and cost.[3] If agents with lower potency and lower genetic barrier to resistance are used, more intensive virologic monitoring is recommended so that therapy can be modified promptly if required. Despite excellent virologic outcomes achieved with oral nucleos(t)ide analogues, limitations still exist including the relatively low rate of HBsAg loss and the potential for drug resistance development. A number of investigators have considered the use of combination nucleos(t)ide therapy as a potential method to improve these endpoints. However, most clinical studies to date have not demonstrated improved outcomes with combination therapy vs. monotherapy and current guidelines do not support this option for the initial treatment of patients with compensated chronic HBV infection. Possible exceptions in which de novo combination therapy may be considered include HIV/HBV coinfection, following liver transplantation and in patients infected with drug-resistant virus.[3]

Recommended Monitoring for Patients Receiving Anti-HBV Therapy

After therapy is started, it is critical that patients be monitored at regular intervals to determine the efficacy of the regimen. This is particularly true when treating with less potent oral nucleos(t)ide analogues, as early treatment failure can be indicative of drug resistance. For newer, more potent agents where the risk of resistance is much lower in treatment-naive patients, regular monitoring continues to be useful in identifying inadequate adherence as well as toxicities.

A panel of expert hepatologists and virologists have published guidelines that include a "road-map" for the on-treatment management of oral nucleos(t)ide analogue therapy based on results of periodic serum HBV DNA testing[3]. According to the recommendations of the road map, serum HBV DNA levels should be evaluated at Week 12 to determine whether primary nonresponse to treatment has occurred, defined as $< 1 \log_{10}$ IU/mL decrease in HBV DNA from baseline. If the patient has been adherent to treatment but has not achieved a primary response at Week 12, treatment should be modified. The next crucial time point for assessment of serum HBV DNA is Week 24 of treatment. Several clinical trials have shown the value of Week 24 HBV DNA level as a predictor of long-term clinical outcomes, virologic efficacy, and drug resistance.[20,27,28] Week 24 responses are classified as complete (HBV DNA negative by PCR), partial (HBV DNA = 60 to < 2000 IU/mL), or inadequate (HBV DNA $\geq$ 2000 IU/mL). An inadequate response indicates the need for a change in treatment, whereas patients with a complete response at Week 24 can continue treatment with monitoring every 6 months. The appropriate course of action for patients who achieve a partial response is dependent upon the resistance profile and antiviral efficacy of the current agent. If the current regimen has a low genetic barrier to resistance, a second drug from a different class should be added. Patients receiving an agent with a high genetic barrier to resistance can continue therapy with monitoring every 3 months. Agents with suboptimal viral efficacy (i.e., delayed viral suppression kinetics associated with adefovir) can also be continued with monitoring at 3 month intervals but only until Week 48, at which point therapy should be changed if a complete response has not been achieved. Once a complete response has been achieved, monitoring should continue at 6 month intervals.

The road map provides useful guidance for on-treatment monitoring and appropriate strategies for addressing suboptimal response with lamivudine, adefovir, and telbivudine. However, the relationship of early virologic response and long-term treatment outcomes with entecavir and tenofovir is less clear. For example, it is clear that a substantial proportion of patients who fail to achieve an initial response during the first 1-2 years of therapy with entecavir may subsequently achieve a response with continued therapy.[29] This may be due to the fact that resistance essentially never develops at such early time points with these agents. Most cases of virologic breakthrough among patients receiving tenofovir in clinical trials have been attributable to nonadherence.[18] Indeed, the 2009 clinical practice guidelines for the management of chronic HBV infection published by EASL recommend that partial virologic response and the need for therapy modification be assessed at Week 48 (rather than Week 24) for patients receiving entecavir, tenofovir, or adefovir treatment.[1] However, a recent retrospective multicenter clinical cohort study from Italy in a predominantly HBeAg-negative population (82%) suggested that baseline HBV DNA level is

significantly associated with the cumulative probability of virologic response (HBV DNA < 12 IU/mL) at month 12 of entecavir therapy (*P* < 0.0001).[24]

Based on the likelihood that suboptimal virologic responses to tenofovir and entecavir at early time points are related to noncompliance with treatment, counseling on the importance of adherence and discussing strategies for overcoming noncompliance are more appropriate approaches than treatment modification. A survey of 301 patients with chronic HBV infection in the United States found that 38% of respondents had missed doses or did not take doses on time on at least 1 occasion each month. The survey identified forgetfulness (45%), running out of medication (14%), the perception that missing 1-2 doses was not important (9%), and avoiding adverse effects (7%) as the most common reasons for noncompliance with HBV therapy.[30] This study also revealed that 37% of responders had not discussed the goals of HBV treatment with their physicians. Therefore, discussing treatment goals and educating patients about the potential benefits of strict compliance to the treatment protocol and the risks associated with nonadherence could provide additional motivation for them to set up strategies for improving adherence such as setting up a daily medication reminder, discussing meal planning, obtaining prescription refills, and considering ways to manage adverse effects other than avoiding therapy.

On-treatment recommendations for patients receiving interferon-based therapy include HBV DNA monitoring every 12-24 weeks during treatment and every 12 weeks during the first 24 weeks of post-treatment follow-up.[2] Among HBeAg-negative patients treated with peginterferon alfa-2a, the rate of undetectable HBV DNA was significantly higher among those with HBV DNA < 80 IU/mL vs. ≥ 80 IU/mL at Week 12 (61% vs 31%, respectively; *P* < .001).[31] However, according to US treatment guidelines, this difference was not sufficiently predictive of long-term outcomes to warrant a change in therapy based on Week 12 response.[3] Recent data showing that Week 12 HBsAg levels are predictive of long-term virologic and serologic response in HBeAg-negative patients receiving treatment with peginterferon alfa-2a ± lamivudine may indicate that other early on-treatment assessments could be useful in this setting.[19]

Treatment Endpoints in HBeAg-Negative Patients

The goal of therapy for chronic HBV infection in both HBeAg-positive and HBeAg-negative patients is long-term virologic suppression without drug resistance in order to prevent or reduce the risk of progressive liver disease. Due to high rates of relapse in HBeAg-negative disease, even after long periods of sustained virologic suppression, and the unavailability of HBeAg seroconversion as a predictive marker for durable post-treatment suppression, the optimal duration of therapy following HBV DNA undetectability in HBeAg-negative disease is very difficult to determine.[32]

Secondary goals of therapy in HBeAg-negative patients include sustained biochemical response (ALT normalization) and HBsAg loss or seroconversion, the latter representing the ultimate indication of therapeutic success and possibly disease cure. Unfortunately, HBsAg seroconversion is extremely rare for HBeAg-negative disease and generally only occurs with interferon-based treatments. Although a small percentage of patients do achieve HBsAg loss with peginterferon alfa-2a therapy, rates of sustained virologic suppression after discontinuation are still < 30%. Discontinuation of nucleos(t)ide analogue therapy is associated with equally high relapse rates.

Fung and colleagues evaluated virologic relapse among 45 HBeAg-negative patients who discontinued lamivudine after 2 years of undetectable HBV DNA while on treatment.[33] The rates of virologic rebound (defined ≥1 $\log_{10}$ copies/mL [~0.2 $\log_{10}$ IU/mL] increase in HBV DNA from end of treatment value) at 24, 36, and 48 months after the discontinuation of treatment were 50%, 62%, and 74%, respectively. Hadziyannis and colleagues conducted an observational study examining a cohort of 33 HBeAg-negative patients from the pivotal adefovir clinical trial who discontinued therapy following 5 years of sustained HBV DNA negativity.[34] All 33 patients experienced increases in HBV DNA to detectable levels after discontinuing adefovir and by 5 years post-treatment, re-initiation of therapy was required in 45.5% of patients because of increased ALT levels. However, HBV DNA returned to undetectable levels in all 54.5% of the other patients who remained off treatment and 10 of these patients (30.3% of the entire cohort) achieved HBsAg loss. Although these data demonstrate that some patients are able to maintain durable virologic suppression after long-term treatment with nucleos(t)ide analogues, most will experience relapse following treatment discontinuation. A recent study reported on HBeAg-negative patients who achieved virologic and biochemical response (HBV DNA < 0.7 MEq/mL (~ 5.3 log10 IU/mL) and ALT < 1.25 times ULN) at Year 1 of entecavir therapy and stopped treatment at that time. Sustained virologic suppression of < 300 copies/mL (~ 59 IU/mL) at week 24 off treatment was seldom observed (3%).[35] Posttreatment outcomes following long-term treatment of HBeAg-negative chronic HBV infection with tenofovir are not yet available. Additional studies are needed to provide clear guidelines on when and if therapy should be discontinued in HBeAg-negative patients treated with nucleos(t)ides.

References

1. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 2009; 50(2):227-242.
2. Lok AS , McMahon BJ. Chronic hepatitis B. Hepatology. 2007;45(2):507-539
3. Keeffe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. Clin Gastroenterol Hepatol. 2008;6(12):1315-1341.
4. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295:65-73.
5. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006;130(3):678-686.
6. Iloeje U, Yang H-L, Su J, et al. HBV viral load less than 10^4 copies/mL is associated with significant risk of hepatocellular carcinoma in chronic hepatitis B patients: an update from the R.E.V.E.A.L.-HBV study. AASLD 2007 Abstract 640.
7. Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. Hepatology 2001;34(4 Pt 1):617-624.
8. Richman DD. The impact of drug resistance on the effectiveness of chemotherapy for chronic hepatitis B. Hepatology. 2000;32(4);866-867.
9. Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004;351(12):1206-1217.
10. Marcellin P, Piratvisuth T, Brunetto M, et al. Virological and biochemical response in patients with HBeAg-negative chronic hepatitis B treated with peginterferon alfa-2a (40kd) with or without lamivudine: results of 4-year follow-up. Program and abstracts of the 43rd Annual Meeting of the European Association for the Study of the Liver; April 23-27, 2008; Milan, Italy. Abstract 103.
11. Marcellin P. HBsAg clearance continues to increase after the end of treatment with PEGASYS ± lamivudine: 5-year follow-up study in patients with HBeAg-negative disease. Program and abstracts of the 19th Annual Meeting of the Asian Pacific Association for the Study of the Liver; February 13-16, 2009; Hong Kong, China. Abstract PE086.
12. Bonino F, Marcellin P, Lau GKK, et al. Predicting response to peginterferon _-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. Gut. 2007;56(5):699-705.
13. Erhardt A, Ludwig AD, Brunetto M, et al. HBV genotypes are the strongest predictors of response to interferon-alfa treatment: multivariate evaluation in 1229 hepatitis B patients. Program and abstracts of the 59th Annual Meeting of the American Association for the Study of Liver Diseases; October 31-November 4, 2008; San Francisco, California. Abstract 883.
14. Moucari R, Mackiewicz V, Lada O, et al. Early Serum HBsAg Drop: a strong predictor of sustained virological response to pegylated interferon alfa-2a in HBeAg-negative patients. Hepatology. 2009;49(4):1151-1157.
15. Brunetto MR, Moriconi F, Bonino F, et al. Hepatitis B virus surface antigen levels: a guide to sustained response to peginterferon alfa-2a in HBeAg-negative chronic hepatitis B. Hepatology. 2009;49(4):1141-1150.
16. Lai CL, Shouval D, Lok AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med. 2006;354(10):1011-1020.
17. Shouval D, Akarca US, Hatzis G, et al. Continued virologic and biochemical improvement through 96 weeks of entecavir treatment in HBeAg(-) chronic hepatitis B patients (study ETV-027). Program and abstracts of the 41st Annual Meeting of the European Association for the Study of the Liver; April 26-30, 2006; Vienna, Austria . Abstract 45.
18. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med. 2008;359(23):2442-2455.
19. Marcellin P, Buti M, Krastev Z, et al. Two year tenofovir disoproxil fumarate (TDF) treatment and adefovir dipivoxil (ADV) switch data in HBeAg-negative patients with chronic hepatitis B (study 102), preliminary analysis. Program and abstracts of the 59th Annual Meeting of the American Association for the Study of Liver Diseases; Oct 31-Nov 4, 2008; San Francisco, California. Abstract 146.
20. Liaw YF, Gane E, Leung N, et al. 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. Gastroenterology. 2009;136(2):486-495.
21. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med. 2008;359(23):2442-2455.
22. Lai CL, Gane E, Liaw YF, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med. 2007;357(25):2576-2588.
23. Kau A, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. J Hepatol. 2008;49:634-651.
24. Lampertico P, Viganò M, Facchetti F, et al. Effectiveness of entecavir for the treatment of NUC-naive chronic hepatitis B patients: a large multicenter cohort study in clinical practice. Program and abstracts of the 59th Annual Meeting of the American Association for the Study of Liver Diseases; October 31-November 4, 2008; San Francisco, California. Abstract 896.
25. Zeuzem S, Gane EJ, Liaw YF et al. Baseline characteristics and early on-treatment response predict the outcomes of 2 years of telbivudine treatment of chronic hepatitis B. J Hepatol. 2009;51(1):11-20.
26. Yuen MF, Fong DY, Wong DK, Yuen JC, Fung J, Lai CL. Hepatitis B virus DNA levels at week 4 of lamivudine treatment predict the 5-year ideal response. Hepatology. 2007;46(6):1695-1703.
27. Yuen MF, Sablon E, Hui CK, et al. Factors associated with hepatitis B virus DNA breakthrough in patients receiving prolonged lamivudine therapy. Hepatology. 2001; 34(4 Pt 1):785-791.
28. Bzowej N, Chan H, Lai CL, et al. A randomized trial of telbivudine (LdT) vs. adefovir for HBeAg -positive chronic hepatitis B: final week 52 results. Program and abstracts of the 57th Annual Meeting of the American Association for the Study of Liver Diseases; October 27-31, 2006; Boston, Massachusetts. Abstract 1005.
29. Sherman M, Rizetto M, Lai C, et al. Long-term follow-up of entecavir treated protocol-defined non-responders in rollover study ETV-901. Program and abstracts of the 58th Annual Meeting of the American Association for the Study of Liver Diseases; November 2-6, 2007; Boston , Massachusetts . Abstract 997.
30. Han SH, Griffith L, Westphalen T. Hepatitis B patient survey: disease understanding and compliance in the United States . Program and abstracts of Digestive Disease Week 2007; May 19-24, 2007; Washington, DC. Abstract S1777.
31. Farci P, Marcellin P, Lu ZM, et al. On-treatment predictors of sustained biochemical and virological response in patients with HBeAg-negative chronic hepatitis B (CHB) treated with peginterferon alfa-2a (40KD)(Pegasys). Program and abstracts of the 40th Annual Meeting of the European Association for the Study of the Liver; April 13-17, 2005; Paris, France. Abstract 484.
32. Leung N. Treatment of chronic hepatitis B: case selection and duration of therapy. J Gastroenterol Hepatol. 2002;17(4):409-414.
33. Fung SK, Wong F, Lok AS. Long-term follow-up of Chinese patients with HBeAg-negative chronic hepatitis B who discontinued treatment after two years of lamivudine monotherapy. Program and abstracts of the 58th Annual Meeting of the American Association for the Study of Liver Diseases; November 2-6, 2007; Boston, Massachusetts. Abstract 972.
34. Hadziyannis S, Sevastianos V, Rapti I, et al. Outcome of HBeAg-negative chronic hepatitis B (CHB) 5 years after discontinuation of long term adefovir dipivoxil (ADV) treatment. Program and abstracts of the 44th Annual Meeting of the European Association for the Study of the Liver; April 22-26, 2009; Copenhagen, Denmark. Abstract 18.
35. Shouval D, Lai CL, Chang TT, et al. Relapse of hepatitis B in HBeAg-negative chronic hepatitis B patients who discontinued successful entecavir treatment: the case for continuous antiviral therapy. J Hepatol. 2009;50(2):289-295.