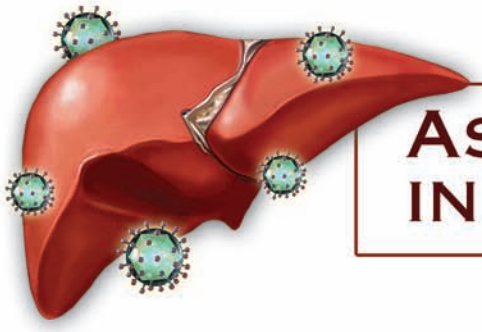

44th Annual Meeting of the European Association for the Study of the Liver

ASSESSING BEST PRACTICES IN HBV THERAPY

A Certified CME/CE Update

Rush University Medical Center
Independent coverage of 2009 EASL*

APRIL 2009

INTENDED AUDIENCE

This program will be of interest to primary care providers and infectious disease specialists who provide care to patients with hepatitis B.

LEARNING OBJECTIVES

Upon the completion of this CME activity, the participant should be able to:

- Discuss significant developments in the diagnosis and management of hepatitis B
- Summarize new drugs and treatment strategies for hepatitis B
- Describe recent hepatitis therapy toxicity, drug interaction and side effect data and strategies for management
- Identify new therapeutic strategies to avoid or overcome antiviral resistance
- Highlight diagnosis and management approaches for hepatitis B in individuals co-infected with HIV

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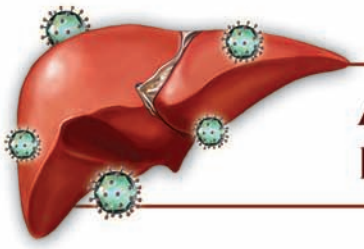

Assessing Best Practices in HBV Therapy

A Certified CME/CE Update

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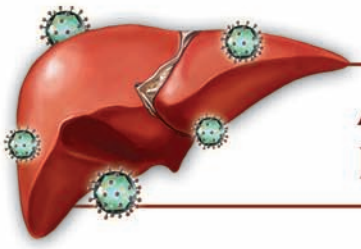


Assessing Best Practices in HBV Therapy

A Certified CME/CE Update

INTRODUCTION

The 44th Annual Meeting of the European Association for the Study of the Liver (EASL) was held in Copenhagen, Denmark, from April 22-26, 2009. Presentations at this conference, which brings prominent clinicians and scientists interested in the field of liver research together, provided some significant new insights into treatments for patients infected with hepatitis B virus (HBV), the most important of which are briefly summarized in this newsletter.

EPIDEMIOLOGY AND NATURAL HISTORY

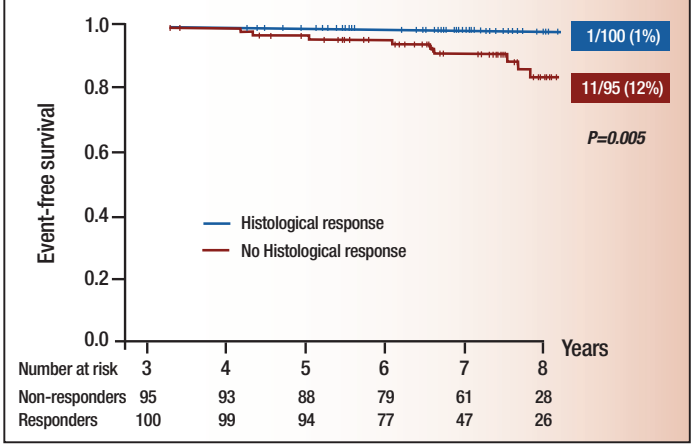
Evaluation of the Importance of Histological Response to HBV Therapy

Most trials on chronic hepatitis B (CHB) have used short-term surrogate endpoints to show efficacy. It is unclear whether these endpoints reflect long-term prognosis. In a study presented at EASL, researchers evaluated long-term histologic response and cirrhosis regression in 195 CHB patients prospectively enrolled in four drug trials. [Wong V, et al. Abst. 235] Histologic response was defined as a reduction of modified Knodell score by 2 points or more with no deterioration in fibrosis.

One hundred (51%) patients achieved histologic response. Event-free survival at 5 years was 99% and 85% in patients with and without histologic response, respectively (Figure 1). Liver-related complications occurred in 1 (1%) patient with histologic response vs. 11 (12%) patients without histologic response ($p=0.005$). Fifteen (60%) of 25 patients with cirrhosis at baseline had regression of cirrhosis and none of them developed liver-related events or died. In contrast, 3 cirrhotic patients without regression of cirrhosis developed HCC, 1 required liver transplantation, and 1 died.

These findings indicate that histologic response—particularly regression of cirrhosis—in CHB patients is associated with improved survival and decreased liver-related complications.

Figure 1. Survival in patients with and without histological response to antiviral therapy



LIVER DISEASE MARKERS

Non invasive markers of liver fibrosis allow fast, non-invasive, repetitive assessment of liver fibrosis compared to traditional liver biopsy. Fibroscan, which measures liver stiffness by ultrasound, is a promising technology that does not have FDA approval but is widely used in Europe. This year at EASL, several studies suggested new indications for the use of these markers of fibrosis.

Fibrosis in HBeAg-positive Patients

Among patients with hepatitis B e antigen-positive (HBeAg-positive) HBV, it can be difficult to differentiate advanced liver fibrosis when alanine aminotransferase (ALT) is normal. A study was designed to determine the clinical factors that could predict advanced liver fibrosis in HBeAg-positive CHB. [Chan HL, et al. Abst. 350] In the study, 453 treatment-naïve, HBeAg-positive patients were referred for liver stiffness measurement (LSM) by transient elastography. Insignificant and advanced fibrosis were defined as LSM ≤6.0 kPa and >9.0 kPa, respectively, when ALT was normal and ≤7.5 kPa and >12.0 kPa, respectively, when ALT was elevated (up to 5x upper limit of normal [ULN]).

Among 74 patients who had liver biopsy, the LSM cut-offs had 90% sensitivity to exclude and 95% specificity to confirm F3-4 fibrosis. Based on LSM, 216 (48%) patients had insignificant fibrosis and 102 (30%) patients had advanced fibrosis. On multivariate analysis, age and ALT—but not male gender, obesity, or HBV DNA—were independently associated with LSM. On receiver operating characteristics (ROC) curve analysis, the risk of advanced liver fibrosis increases significantly in HBeAg-positive patients as young as 35 years of age and ALT >0.5x ULN.

Fibrotest and Fibroscan for HBsAg Inactive Carriage

HBsAg inactive carrier state is characterized by very low or undetectable HBV DNA levels, HBeAg negativity, and normal ALT. However, in the absence of liver biopsy, this status can be difficult to distinguish from HBeAg-negative CHB. Researchers studied the potential of noninvasive tests as a diagnostic tool. [Hilleret M, et al. Abst. 361] For each patient, both transient elastography (Fibroscan) and Fibrotest were performed. When compared to CHB patients, inactive carriers were significantly younger (37 vs. 41 years; $p<0.01$) and had lower ALT serum levels (26 IU/ml vs. 88 IU/ml; $p<0.0001$), HBV DNA (379 vs. 2042 IU/ml; $p<0.0001$), Fibrotest values (0.15 vs. 0.28; $p<0.0001$), and Fibroscan values (4.9 vs. 8.1 Kpa; $p<0.03$).

In inactive carriers, Fibrotest indicated F0 (<0.21) in 81.6% of cases. Among them, 95.6% had a Fibroscan score lower than 7 Kpa, confirming the absence of significant fibrosis. In the 17 patients with Fibrotest >0.21, 5 (29.4%) had Fibroscan higher than 7 Kpa. These patients had Fibrotest ranging from 0.23 to 0.33 and Fibroscan from 7.2 to 10.4 Kpa.

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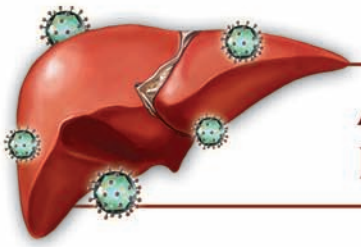


They were significantly older (50 vs. 35 years, $p<0.03$) than patients without fibrosis.

Fibrotest (indicating F0) has an excellent specificity for the diagnosis of HBsAg inactive carrier state and may be a first line fibrosis marker.

HBsAg as a CHB Disease Marker

HBsAg positivity indicates chronic HBV infection. HBsAg clearance improves liver disease prognosis and is expected to occur naturally in HBV infected patients at a rate of less than 2% annually. [Chu CM, et al. *Hepatology* 2007;45:1187-92] HBsAg serum level is a new clinical marker and quantification is now available due to the development of commercial assay systems. Several studies using quantification of HBsAg titers were presented this year defining the natural history of CHB.

HBsAg was quantified in 162 HBV-monoinfected patients (54 HBeAg-positive, 108 HBeAg-negative) who were not currently being treated. [Jaroszewicz J, et al. Abst. 364] Patients were grouped into four HBV-infection phases: HBeAg-positive Immune tolerant (IT), HBeAg-positive immune clearance (IC), HBeAg-negative low replicative (LR), and HBeAg-negative reactivation phase (RE).

Median HBsAg levels showed significant differences between consecutive CHB phases. The highest levels were seen in the IT and IC groups, the lowest was seen in the LR group, and intermediate levels were seen in the RE group. HBsAg level was independently associated with age ($p< 0.01$), HBV DNA quantity ($p< 0.001$), and platelet count ($p=0.03$). By following selected HBeAg-positive patients in the immune clearance phase, the investigators found associations between HBsAg-kinetics and HBeAg-seroconversion suggesting a potential clinical utility for predicting HBeAg and HBsAg loss and seroconversion during the natural course of infection.

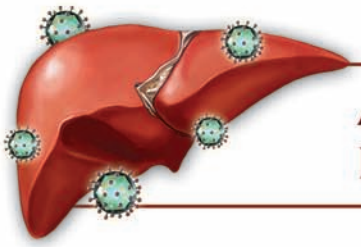
In another study, serum HBsAg and HBeAg titers were measured during immune tolerance, immune clearance, immune control, and immune escape. [Nguyen T, et al. Abst. 370] The HBsAg titers were significantly higher in the HBeAg-positive phases and lowest in the immune control phase ($P< 0.05$). The HBeAg titer was higher in the immune tolerant phase, and a very low viral load and low HBsAg titer were found in the immune control phase ($P< 0.05$). The immune control phase was characterized by HBsAg titers of 3 $\log_{10}$ IU/mL. Since this study demonstrates clearly that HBsAg and HBeAg titers significantly change over the natural history of CHB, and the immune control phase of CHB is characterized by HBsAg titers of 3 $\log_{10}$ IU/mL, the authors suggested that this cutoff might serve as a useful therapeutic endpoint during antiviral therapy.

Update from the REVEAL HBV Study

The risk of CHB disease progression is thought to be greatest after 40 years of age; however, the risk of hepatocellular carcinoma (HCC) in younger patients is unknown. Researchers in Taiwan analyzed a subset of the REVEAL-HBV study cohort who were <40 years of age at entry. [Yang HI, et al. Abst 384] HCC diagnosis was determined through data from the National Cancer Registry and Death Certification System in Taiwan. The study included 1,216 subjects with a median age of 35 years. After a median of 12 years, 16 subjects (all males) developed HCC for an incidence rate of 111/100,000 person-years of follow-up. Elevated serum ALT and cirrhosis were independent predictors of HCC. Compared to a serum ALT < 15 IU/L, subjects with baseline serum ALT 15-44 and ≥45 had an adjusted hazards ratio of 3.0 and 8.3, respectively. Cirrhosis at baseline was associated with an increased risk of HCC, with an adjusted hazard ratio of 12.5. Alcohol consumption, older age, increasing serum HBV DNA, and HBeAg-positive status were all associated with a trend towards higher HCC risk, but these were not statistically significant. This emphasizes the importance of screening for HCC in patients younger than 40 years of age, and especially those patients with characteristics that may place them at higher risk for HCC.

Triple Infection with HBV, HCV, and HIV

The natural history and treatment for individuals who are infected with a combination of HBV, HCV, and HIV has not been extensively studied. Researchers studied progression among HIV-infected only patients, HBV/HIV-infected patients, HCV/HIV-infected patients, and triple-infected patients from the ATHENA observational HIV cohort. [Arends J, et al. Abst. 388] Among the 11,181 patients in the analysis, 6% (n=682) were HBV/HIV-infected, 7% (n=769) were HCV/HIV-infected, and 1% (112) were triple-infected. During a median follow-up of 5.8 years, 9% (818) of patients died. Triple-infected patients and HCV/HIV-infected patients died significantly faster than HIV-infected only patients ($p< 0.001$), while time to death did not differ between HBV/HIV-infected and HIV-infected only patients ($p=0.30$). Compared with HIV-infected only patients, triple-infected patients had an 86% increased risk of dying and HCV/HIV-infected patients had a 50% increased risk of dying. These data, which involve an unusually large number of HIV/HCV/HBV triple-infected patients demonstrate that these patients, as well as HCV/HIV-infected patients, have a significantly increased risk of death relative to HIV-infected only and HIV/HBV-infected patients. These findings indicate that HCV treatment should receive priority in HIV-infected patients who are co-infected with HCV, whether doubly and triply infected.



THERAPEUTIC STRATEGIES

Seven drugs are now available and approved by the FDA for the treatment of CHB. They include conventional interferon alpha (IFN), pegylated interferon alpha (PegIFN) and 5 nucleos(t)ide analogues: lamivudine (LAM), telbivudine (LdT), entecavir (ETV), adefovir (ADV) and tenofovir (TDF). A number of presentations at EASL provided new data regarding these therapies.

HBV Drugs in Pregnancy

High maternal serum HBV DNA is a risk factor for vertical transmission of HBV. LAM (US pregnancy category C) and TDF (US pregnancy category B) are licensed for the treatment of both HIV-1 and chronic HBV infection. This study queried the Antiretroviral Pregnancy Registry (APR) to detect major teratogenic effects involving antiretrovirals (ARVs) and HBV drugs administered in pregnancy. [Brown RS, et al. Abst. 3] Cumulative APR data on HBV drug exposure in pregnancy for LAM, and TDF were reviewed from 11,950 prospective cases. Congenital anomaly rates with LAM and TDF were comparable to those in the CDC population-based birth defects surveillance system in the US (2.72/100 live births) and to rates of other ARVs in the APR. Thus, no overall increase in prevalence or any specific pattern of congenital anomalies has been detected with the use of LAM or TDF through prospective voluntary reporting to the APR. For the other therapies approved for HBV, there was insufficient data available in the registry to allow for a risk analysis.

Comparison of Treatments for CHB in HBeAg-Positive Patients

A study used sophisticated statistical analysis to estimate the relative effectiveness of therapies for CHB in HBeAg-positive patients. [Woo G, et al. Abst. 931] A treatment comparison method was used for 10 treatment strategies from 12 trials with LAM as the reference treatment. In this comparison, TDF had the highest predicted probability of undetectable HBV DNA at 86% (95% CI: 59%-98%), followed by ETV at 58% (28%-85%). LAM + ADV had the highest probability of ALT normalization, followed by TDF. PegIFN had the highest probability of HBeAg seroconversion at 25% (14%-36%), followed by combination therapy with LAM and PegIFN at 24% (14%-39%). TDF had the highest probability of HBsAg loss at 19% (0-93%), followed by PegIFN + LAM. ETV had the highest probability of improving liver histology at 56% (8%-93%), followed by PegIFN at 50% (4%-93%). No treatment strategy was significantly superior for all outcomes at one year, though both TDF and ETV ranked highly in this analysis.

ENTECAVIR

ETV in Treatment-naïve CHB Patients

In this real world study, 272 patients (84% HBeAg-negative, 49% cirrhotics) were recruited and treated with ETV 0.5 mg daily for 16 months. [Lampertico P, et al. Abst. 916] Ninety-five percent of the patients achieved an undetectable HBV DNA at week 72 and significantly faster in patients with lower viremia. Among patients with >8 $\log_{10}$ IU/mL HBV DNA at baseline, 77% became HBV DNA negative at week 72, compared with 96% of those with baseline viremia between 5 and 8 $\log_{10}$ IU/mL and 100% of those with less than 5 $\log_{10}$ IU/ml at baseline ($p < 0.001$). There was no virologic breakthrough during the study, and 86% normalized their ALT levels. HBsAg titers were also assessed in 78 patients and remained unchanged during therapy for the majority of patients; however, 17% had a >0.5 $\log_{10}$ IU/ml decrease and 3 patients lost HBsAg. Liver stiffness, assessed by Fibroscan in 73 patients, decreased from 9.3 (4-29) to 7.0 (5-24) KPa, with ≥2 point decrease in 64% of the patients. In addition, 68% of patients with baseline >12.5 KPa had decreased liver stiffness levels by the end of the study. This study indicates that ETV is an effective treatment option for nucleos(t)ide analogue–naïve patients in real world practice, performing as well as when tested in registration trials.

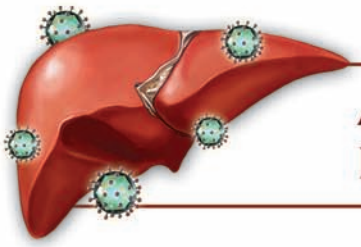
Peginterferon alfa-2a vs ETV

A randomized, open-label study compared the efficacy and safety of PegIFN with ETV in HBeAg-positive CHB patients with normal and mildly elevated baseline ALT levels. [Chen XP, et al. Abst. 904] In this study, treatment with PegIFN was significantly superior to ETV regarding on-treatment decline in HBeAg at both 24 and 48 weeks ($p<0.001$ and $p=0.001$), rate of HBeAg seroconversion (41.2% vs 12.1%, $p=0.007$), decline in HBsAg at weeks 24 and 48 ($p=0.004$ and $p=0.0061$), clearance of HBsAg at week 48 (10% vs 2%) and HBsAg seroconversion rate (6% and 0%, $p<0.05$). The proportion of patients who achieved HBV DNA < 1000 copies/ml at week 48 was similar in the 2 groups: 65% in the PegIFN group vs 70% in the ETV group. These data indicate that PegIFN is superior to ETV in achieving HBeAg seroconversion and in reducing HBeAg and HBsAg levels in HBeAg-positive CHB patients with normal or mildly elevated ALT levels.

TELBIVUDINE

Prolonged Efficacy and Safety of Telbivudine – the Globe Study

The GLOBE and 015 studies demonstrated that LdT had superior efficacy to LAM in adult patients with HBeAg-positive and HBeAg-negative CHB. A total of 530 LdT-treated patients without genotypic resistance at the end of these studies were enrolled into the 2303 rollover study without drug discontinuation. [Hsu CW, et al. Abst. 911] The per protocol population of 503 patients was considered for this analysis. At 3 years, among 293 HBeAg-positive patients, 75% had undetectable HBV DNA (< 300 copies/mL) and 83% had ALT normalization. Of the HBeAg-positive patients, 55% obtained HBeAg loss and 39% achieved HBeAg seroconversion, while 4 (1.5%) lost HBsAg and 1(0.4%) had HBsAg seroconversion. Of the 210 HBeAg-negative patients, 85% had undetectable HBV DNA and 84% had ALT normalization at 3 years. Higher rates of PCR negativity (87%) and seroconversion (47%) were achieved



at 3 years in patients who had undetectable HBV DNA at week 24 of the core studies. The cumulative HBeAg seroconversion rate for 3 years was 54%. The LdT safety profile was similar to the 2-year results. Thus, 3 years of LdT treatment provided effective viral suppression and ALT normalization in HBeAg-positive and HBeAg-negative CHB patients. HBeAg-positive patients receiving LdT achieve a high rate of seroconversion, especially patients with favorable baseline characteristics.

TENOFOVIR

TDF in Patients with HBV-Induced Cirrhosis

An efficacy and safety analysis was performed of the subset of cirrhotic patients receiving TDF for 96 weeks in two phase 3 CHB registration trials, GS-102 and GS-103. [Buti M, et al. Abst. 21] Eighty-one of 426 patients (19%) originally randomized to TDF were cirrhotic (47 HBeAg-negative and 34 HBeAg-positive) with median baseline HBV DNA of 7.58 $\log_{10}$ copies/mL and ALT of 92 U/L. Similar proportions of cirrhotic (90% intent-to-treat and 97% observed) and non-cirrhotic (85% intent-to-treat and 95% observed) patients suppressed HBV DNA to < 400 c/mL (<69 IU/mL) at week 96. Among patients who remained on treatment, 83% of cirrhotic and 78% of non-cirrhotic patients had normal ALT at week 96 with median values of 30 and 29 U/L, respectively. Of 29 cirrhotic HBeAg-positive patients with week 96 serology results, 9 seroconverted to anti-HBe (31%) and 2 seroconverted to anti-HBs (both genotype D).

Grade 3 and 4 adverse events occurred in 11% of cirrhotic and 13% of non-cirrhotic patients, and serious adverse events occurred in 15% and 9%, and grade 3/4 laboratory abnormalities in 31% and 23%, respectively. One cirrhotic patient developed HCC. No cirrhotic patient experienced an increase in creatinine of 0.5 mg/dL, creatinine clearance < 50 mL/min, or hepatic decompensation.

This analysis demonstrates that the efficacy and safety of TDF at 96 weeks is not influenced by the presence of cirrhosis at onset of therapy. Further, these data support the conclusion that TDF antiviral effects against HBV are comparable in both cirrhotic and non-cirrhotic patients.

Characteristics of HBeAg-Positive Patients with HBsAg Loss/Seroconversion after TDF Treatment

The GS-103 study in HBeAg-positive patients found that HBsAg loss occurred more frequently in TDF-treated patients than in ADV-treated patients at week 48: 3.2% TDF vs. 0% ADV (p=0.02). Researchers sought to determine which patient characteristics are associated with HBsAg loss in TDF-treated patients. [Heathcote EJ, et al. Abst. 909] The trial included 266 patients with HBeAg-positive CHB who were randomized to receive once-daily TDF 300 mg (N=176) or ADV 10 mg (N=90) for 48 weeks. All patients who had a biopsy performed at week 48 were eligible to receive open-label TDF for an additional 7 years.

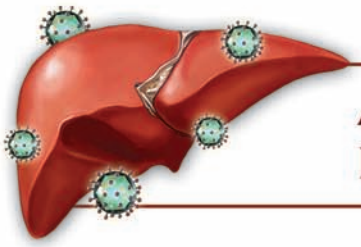
Six percent of the patients in the study (10 TDF-TDF and 5 ADV-TDF) experienced HBsAg loss by week 96 (11 of 15 anti-HBs). Of these 15, 100% were Caucasian, 80% were men, and 80% were from Europe with a median age of 35 years. All patients were naïve to interferon. In patients with HBsAg loss, the median baseline levels of HBsAg were 5.09 $\log_{10}$ IU/mL, HBV DNA were 9.49 $\log_{10}$ copies/mL, and ALT were 163 U/L. The median pretreatment Knodell necroinflammatory score was 9.0 and sixty-seven percent had bridging fibrosis or cirrhosis prior to treatment. Fifty-seven percent harbored genotype A, and 43% harbored genotype D virus. Most patients lost HBeAg prior to HBsAg loss. Although no patient in the ADV arm achieved HBsAg loss within the first 48 weeks, by week 96 (after 48 weeks of open-label TDF) the same percentage of patients in the TDF-TDF and ADV-TDF arms achieved HBsAg loss; however, no ADV-TDF patient achieved HBsAg loss until week 80 or later.

This analysis indicates that TDF induces loss of HBsAg most frequently in Caucasian patients infected with genotype A or D virus and patients with high HBV DNA and high HBsAg levels prior to treatment.

Safety and Tolerability of TDF

Another analysis was conducted of data from the GS-102 and GS-103 studies, specifically of safety and tolerability data from week 96 of 389 patients treated with TDF. [Marcellin P, et al. Abst. 925] Following 96 weeks of TDF treatment, 7 (1.8%) of patients experienced some adverse event considered related to the study drug; however, no patient experienced a grade 3 or 4 adverse event and adverse events resulting in TDF discontinuation occurred in only 3 (< 1%) patients. The reasons for discontinuation in the 3 patients who discontinued for an adverse event included malignant hepatic neoplasm, creatinine increase (peak 1.3 mg/dL) and disturbance in attention, fatigue, and dizziness.

Grade 3 and grade 4 laboratory abnormalities occurred in 8.7% of patients during open-label TDF and those occurring in >1% of patients included glucosuria (2.8%), elevated serum amylase (1.5%), and elevated prothrombin time (1.8%). During open-label TDF, no TDF patient treated for 96 weeks had a confirmed decrease in creatinine clearance to < 50 mL/min, increase in creatinine of 0.5 mg/dL, or graded serum creatinine abnormality. No patient experienced bone fractures related to TDF. These data demonstrate that TDF is extremely well-tolerated for 2 years in patients with CHB.



NEW THERAPIES AND STRATEGIES

NOVEL AGENTS

With the discontinuation of clevudine (CLV) development, as discussed below, there are no new drugs for CHB in advanced clinical development. Therefore, clinicians should carefully consider the therapeutic strategies used in the treatment of CHB to maximize efficacy and preserve future options.

Mitochondrial Toxicity/myositis observed with CLV exposure

While data presented at this conference demonstrated that CLV monotherapy has antiviral activity against HBV comparable to ETV [Shin SR, et al. Abst. 22], recent data suggests that longer term exposure may lead to adverse effects, specifically a myopathy related to mitochondrial toxicity. Park and co-workers reported the development of mitochondrial myopathy in 2 patients followed in a cohort of 123 CHB patients receiving CLV for more than 48 weeks to define the long-term safety of CLV therapy. [Park SY, et al. Abst. 926] In the 2 patients, the myopathy developed after 52 and 60 weeks of CLV exposure and occurred in a 40-year-old male with proximal limb weakness and a 39-year-old female who was unable to stand up by herself. Both patients had biochemical evidence of myositis as evidenced by markedly elevated levels of serum creatine kinase (1333 IU/L and 721 IU/L, respectively), serum myoglobulin (373 ng/mL), serum LDH levels (894.3 IU/L and 2750 IU/L, respectively), and elevated serum lactic acid levels (8.2 mmol/L). The clinical and biochemical findings were confirmed by electrophysiological analysis and muscle biopsies. Biopsy revealed myonecrosis associated with numerous ragged red fibers and predominant type II fiber atrophy which confirmed the diagnosis of mitochondrial myopathy. After discontinuation of CLV, both patients experienced normalization of biochemical markers of myositis and slowly recovered motor strength, suggesting that these adverse effects are reversible with drug withdrawal. In light of this report, a published case series of seven CLV treated patients [Seok JI, et al. *Hepatology* March, 2009 (Epub ahead of print)] and other cases observed in the ongoing phase III clinical trials, the sponsor of these international studies, in conjunction with its independent Data Safety Monitoring Board, voluntarily terminated the clinical development of CLV for the treatment of CHB in April, 2009.

Chinese Herbal Formula for the Treatment of CHB

Over many years, plants of the genus Phyllanthus have been used in the aqueous extract form as traditional remedies for the treatment of CHB in China and India. Studies suggest that the mechanism of action of *P. amarus* may be related to inhibition of HBV polymerase activity. Thyagarajan and colleagues previously reported that 59% of 37 patients with CHB cleared detectable HBV DNA 2–3 weeks after the end of a 30 day treatment period with *P. amarus*. [Thyagarajan SP, et al. *Lancet* 1988;2:764–766]

In a well-designed, randomized, double-blind, placebo-controlled trial the anti-viral effects of a Chinese Herbal Formula (Phyllanthus Compound) in 90 patients with CHB were investigated. [Zhou DQ, et al. Abst. 933] Patients who were HBeAg-positive and had serum HBV DNA levels greater than 7 $\log_{10}$ copies/ml were randomized (2:1) to receive Phyllanthus Compound (n=60) or placebo (n=30) for 48 weeks. HBV viral suppression was significantly greater among patients who received the Phyllanthus Compound (3.4 $\log_{10}$ copies/mL) compared to those who received placebo (0.1 $\log_{10}$ copies/mL) ($P<0.01$). Further, undetectable HBV DNA (<3 $\log_{10}$ copies/mL) was achieved in 13 of the 60 patients (21.7%) in the Phyllanthus group compared to only 1 of the 30 patients (3.3%) in the placebo group ($P < 0.01$). HBeAg loss and seroconversion were observed more frequently in patients receiving the Phyllanthus compound than placebo (HBeAg loss: 12/60 [20%] vs. 1/30 [3.3%]; Seroconversion: 9/60 [15%] vs. 0/30 [0%]). While preliminary, these data suggest that Phyllanthus Compound may be effective for the treatment of CHB, resulting in viral suppression and HBeAg seroconversion in some patients.

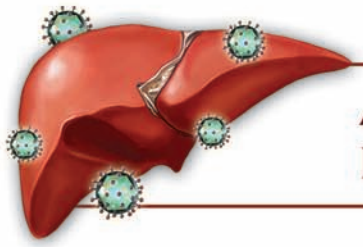
Anti-HBV activity of Simvastatin and Synergistic Interactions with oral nucleos(t)ide analogues

Although not in clinical trials, another potential treatment may be the use of HMGCoA reductase inhibitors (statins). Bader and colleagues have previously reported that simvastatin (SIM) has significant antiviral activity in vitro against wild-type and drug resistant HBV with inhibition of both extracellular virions and intracellular DNA intermediate forms. Building on these observations, a study was performed to assess the antiviral activity of combinations of SIM plus LAM, ADV or TDF and to determine potential additive or synergistic effects. [Bader T, et al. Abst. 552] Using a Hep2.2.15 cell line model, the investigators reported that the combination of SIM with LAM or TDF demonstrated a moderately synergistic antiviral effect. In contrast, the combination of SIM and ADV resulted in additive antiviral effect against HBV replication. Although these combinations have not been tested *in vivo*, these findings suggest the potential role for the combination of currently available HBV agents with the generically available statins, including drugs like SIM.

NEW THERAPEUTIC STRATEGIES

Combination of Entecavir and Tenofovir is effective in CHB patients with extensive prior anti-viral treatment

ETV and TDF are potent antiviral agents for HBV with high genetic barriers to the development of resistance. Further, these drugs have distinct viral mutation patterns and cross-resistance is not observed. There are limited data, however, on the combination of these potent drugs. To investigate the effectiveness of combination therapy with ETV and TDF, researchers in India conducted an open-label pilot study [Amarapurkar D, et al. Abst. 901] which involved 8 patients with



HBV-related decompensated liver cirrhosis. Three patients were treatment experienced (LAM and LAM + ADV) and 5 patients were treatment-naïve. Patients were given ETV 0.5 mg and TDF 300 mg daily. The pretreatment mean HBV DNA was 6.11 $\log_{10}$ copies/ml and mean Child-Turcotte-Pugh score was 9.6. After a mean treatment period of 4.87 months, the mean HBV DNA was 2.54 $\log_{10}$ copies/ml and 5 patients had an undetectable HBV DNA. More importantly, the liver disease improved, with the Child-Turcotte-Pugh score decreasing to 6.5 with therapy. No adverse events were reported.

In a second study, the safety and efficacy of TDF + ETV in treatment experienced CHB patients with advanced liver disease were investigated. [Lütgehetmann M, et al. Abst. 922] In this single center cohort, the median treatment duration was 10 months and was associated with a statistically significant median HBV DNA decline of 3.2 $\log_{10}$ copies/ml. Further, the majority (13 of 15) became HBV DNA undetectable, including 9 patients who had never previously achieved an undetectable HBV DNA despite prior, long-term antiviral treatment (median 55 months).

Although additional studies are needed, these studies suggest that ETV + TDF may be an effective rescue therapy in CHB patients harboring complex viral resistance patterns.

HBsAg is an important marker of HBV therapeutic response

The long-term (5-year), post-treatment results of a large, randomized, multinational study that treated HBeAg-negative patients with 48 weeks of PegIFN with or without LAM were reported. [Marcellin P, et al. Abst. 924] Patients received PegIFN (n=177); PegIFN + LAM (n=179) or LAM (n=181) during the initial 48 week treatment period. The long-term follow-up study included 230/356 (64.6%) of those treated with PegIFN ± LAM and 85/181 (47.0%) patients treated with LAM alone. Five years post-treatment, overall virologic response rates in patients treated with PegIFN ± LAM were: HBV DNA < 10,000 copies/mL (~2,000 IU/mL): 21% (51/230); HBV DNA < 400 copies/mL, 17% (38/230). Importantly, HBsAg clearance and seroconversion rates increased steadily over time in patients treated with PegIFN ± LAM and at 5 years post treatment, 12.2% of these patients had cleared HBsAg compared with only 3.5% of patients treated with LAM alone (P=0.02). These data suggest the PegIFN is associated with HBsAb seroconversion in patients who are HBeAg-negative.

The role of quantitative HBsAg measurement was further assessed in a study that treated 79 CHB patients (37 HBeAg-positive and 42 HBeAg-negative) with combination of PegIFN and ADV for 48 weeks to establish markers of response during and after treatment. [Takkenberg B, et al. Abst. 15] The combination of PegIFN and ADV induced HBsAg loss in 20% of patients. Among HBeAg-negative patients, pre-treatment HBsAg level predicted subsequent HBsAg loss (PPV 85%). Among HBeAg-positive patients, decline of HBsAg at week 12 was significantly higher in patients who cleared HBsAg. These data suggest that measurement of HBsAg level at baseline and during treatment may be important tools in the management of CHB patients.

RESISTANCE

TESTING

HBV Mutants in Untreated and LAM-Resistant Patients

HBV mutants with resistance to specific nuclueos(t)ide analogues may pre-exist in treatment-naïve patients. To evaluate the prevalence of resistance, researchers analyzed the genetic variability of the entire HBV reverse transcriptase (RT) domain and of the overlapping S gene in 100 treatment-naive and 59 LAM-resistant, CHB patients. [Pollicino T, et al. Abst. 927]

In the naïve group, no previously reported RT primary mutation was detected, but sequencing revealed variably combined secondary mutations potentially associated with resistance to antivirals in 46 cases (46%). Moreover, 4 cases carried mutations modifying the S protein antigenicity. In the LAM-resistant group, in addition to the typical primary LAM-resistant mutations, various combinations of primary and secondary mutations conferring resistance to other nucleos(t)ide analogues were detected in 41 cases (69.5%). The LAM-resistant isolates carried relevant S gene mutations in 11 cases (19%) with deep modification of the S protein antigenicity in 9 cases and development of stop codons in 2 cases. This study shows that HBV mutants associated with drug resistance may be present in treatment-naive patients and that variants emerging during LAM treatment may also carry mutations that confer resistance to other antivirals and alter S protein immunoreactivity. Moreover, mutations that overlap with S gene may compromise the effect of the HBV vaccine.

RESISTANCE DEVELOPMENT AND EFFECT OF RESISTANCE ON ACTIVITY

Anti-HIV Activity of Telbivudine

Currently, there are limited treatment options for chronic HBV in HIV/HBV co-infected patients. Most approved oral anti-HBV agents have the potential of inducing HIV resistance in patients co-infected with HIV and HBV who do not require anti-HIV treatment. Prior *in vitro* testing with LdT has shown no activity against HIV. Researchers designed a study to determine the *in vitro* anti-HIV activity of LdT, using ETV as a positive control. To do so, they used the PhenoSense™ HIV assay (Monogram Sciences) to measure viral replication 48 hours after infection. [Avila C, et al. Abst. 551]

Eight different wild-type HIV clinical isolates representing different geographic locations and viral subtypes as well as 2 HIV multi-drug resistant isolates were assessed for drug susceptibility to LdT and ETV.

LdT did not exhibit *in vitro* anti-HIV activity (IC_{50} values >600 µM) against any of the HIV isolates. In contrast, ETV exhibited antiviral activity against most of the clinical HIV isolates at IC_{50} values ranging from 7.62 to 15.09 µM, and the IC_{50} increased >8-fold in HIV isolates harboring the M184V mutation.

This study confirmed prior data demonstrating in vitro ETV activity against HIV while confirming prior results that LdT has no antiviral effect against a broad range of wild-type and multi-drug resistant HIV isolates. The results support further investigating the anti-HBV efficacy and safety of LdT in HIV-HBV co-infected patients who do not require anti-HIV treatment.

Peginterferon Alfa-2a vs ADV in LAM-Resistant Patients

Rescue therapies for LAM-resistant CHB are limited due to cross-resistance profiles of nucleos(t)ide analogues. A randomized, open-label study compared the efficacy and safety of PegIFN with ADV in HBeAg-positive patients with LAM-resistant CHB. [Hou JL, et al. Abst. 910] This study included 235 patients with documented LAM-resistance who were randomized (2:1) to receive either PegIFN (180 µg/week for 48 weeks followed by 24 weeks of treatment-free follow-up) or ADV (10 mg daily). LAM was continued for the first 12 weeks, and response was assessed at week 72.

The results at 72 weeks are shown in table 1. While HBeAg loss was similar between the 2 arms, HBeAg seroconversion was significantly higher in the PegIFN arm. Of the 18 patients treated with PegIFN who achieved HBeAg seroconversion, 3 (16.7%) achieved HBsAg seroconversion. Decline in HBsAg titer (qHBsAg, Abbott Architect assay) from baseline to weeks 24 and 48 was significantly greater with PegIFN than with ADV (Week 24: 0.75 vs. 0.31; Week 48: 0.92 vs. 0.35; both $P < 0.001$) and HBsAg decline was associated with HBeAg loss in PegIFN-treated patients.

This study demonstrated efficacy of PegIFN in LAM-resistant patients. As seen in HBV treatment-naïve patients, this study confirmed the correlation between decline in HBsAg titers and HBeAg loss and HBsAg seroconversion. PegIFN may represent an alternative therapy in patients who develop LAM resistance.

Table 1. PegIFN vs. ADV Comparison

Results (at 72 weeks)	PegIFN (48 week treatment) N=155 (%)	ADV (72 weeks treatment) N=80 (%)	*P* value
HBeAg loss	21 (13.6%)	7 (8.8%)	0.282
HBeAg seroconversion	18 (11.6%)	3 (3.8%)	0.045
HBsAg loss	5 (3.2%)	0	0.169
HBsAg seroconversion	3 (1.9%)	0	0.552

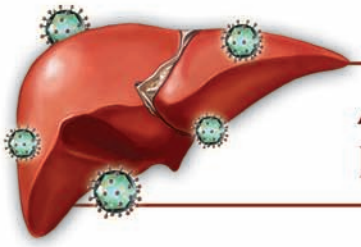
High Genetic Barrier of ETV to HBV resistance through 6 years of follow up of treatment naïve patients

ETV is a potent HBV viral therapy with relatively high genetic barrier to resistance. A study presented at this meeting builds on previously reported data, providing follow up results of ETV resistance in treatment-naïve patients through 6 years of treatment. [Brett-Smith H, et al. Abst. 20]

In years 1 through 6, respectively, 663, 278, 149, 120, 108 and 99 nucleos(t)ide-naive patients were treated and monitored, with 94% in year 6 having an HBV DNA <300 copies/mL. No patient in year 6 showed emerging ETV resistance at T184, S202 or M250 ± LAM resistance M204I/V±L180M. The cumulative probability of genotypic ETV resistance in nucleos(t)ide-naive patients remained at 1.2% through 6 years.

Among LAM-refractory patients treated with ETV, 187, 146, 80, 52, 33 and 29 were monitored in years 1 through 6, respectively. The cumulative probabilities of genotypic ETV resistance at years 1 through 6 were 6%, 15%, 36%, 47%, 51%, and 57%, respectively, and of virological breakthrough with ETV resistance was 50% through year 6. Among the 74 (40%) LAM-refractory patients who achieved undetectable HBV DNA on ETV, 5 (7%) subsequently developed ETV resistance.

This study demonstrated that ETV has high potency and resistance remains rare (1.2%) in nucleos(t)ide-naive patients through 6 years. LAM-refractory HBV has a reduced resistance barrier to ETV, and those patients with LAM resistance are likely to benefit from add-on or combination therapy since the risk of the development of ETV resistance in those patients is relatively high.



Assessing Best Practices in HBV Therapy
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