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eViralHepatitis Review
Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Supported by educational grants from Gilead Sciences, Inc. and Vertex Pharmaceuticals

eViralHepatitis Review
December 2011: VOLUME 2, ISSUE 1

Editor's Note:

As we begin Volume 2, we want to welcome back our returning subscribers and say hello to our newly registered clinicians. In Volume 2, we will continue to provide you with current, clinically relevant data important to helping you improve outcomes in your patients, delivered via 7 newsletters and a new feature to this volume: 5 case-based podcasts. Topics scheduled for this volume include: Hepatitis B virus (HBV) and Pregnancy, Extending the hepatitis C virus (HCV) New Data to HIV Coinfection, and Occult HBV.

CONFERENCE COVERAGE OF THE 62ND ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASE

In this Issue...

New information from clinical studies of nucleos(t)ide analog anti-HBV drugs continue to inform the selection, use, and utility of available treatment options for patients with chronic hepatitis B virus (HBV) infection. In this issue we review new findings from chronic hepatitis B treatment studies presented at the 62nd Annual Meeting of the American Association for the Study of Liver Disease (AASLD 2011), including the association of long-term virologic suppression with reversal of fibrosis and cirrhosis in patients receiving tenofovir, the comparability of entecavir monotherapy with entecavir/tenofovir dual therapy, and the long-term safety and efficacy of tenofovir in HIV/HBV coinfected patients.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Discuss new clinical trials findings relevant to the antiviral management of patients with chronic HBV infection
- Describe the histologic effects of long-term virologic suppression in patients with chronic HBV infection
- Discuss new clinical trial findings relevant to the antiviral management of patients with HIV/HBV coinfection

IMPORTANT CME/CE INFORMATION ▼ Program Begins Below

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Release Date
December 15, 2011

Expiration Date
December 14, 2013

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THIS ISSUE

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COMMENTARY

The past 15 years have witnessed excellent progress in the management of chronic hepatitis B (CHB). There are now at least six FDA-approved agents for both HBeAg-positive and -negative chronic HBV infection (tenofovir, entecavir, telbivudine, adefovir, lamivudine, [PEG-] interferon). Nucleos(t)ide analog therapy is capable of producing high

rates of virologic suppression.' With entecavir and tenofovir in particular, monotherapy with each of these agents in treatment-naive persons is associated with very low rates of genotypic and phenotypic drug resistance over many years.[1,2] In the U.S., therefore, these two agents have emerged as first line therapy. Further evidence of the salutary effects of long-term virologic suppression of CHB comes from the study by Marcellin and colleagues, who demonstrate that the great majority of persons on long-term tenofovir therapy who had paired liver biopsies experienced improvement in fibrosis stage; this was true even among those with baseline cirrhosis, a particularly striking finding and further evidence that cirrhosis is a more dynamic state than previously thought. These findings imply that viral suppression can confer clinical benefit in persons with all stages of disease.

Regardless of agent, the major shortcoming of the nucleos(t)ide analog class has been a consistent ceiling on the development of more durable endpoints. For instance, HBeAg seroconversion rates at one year of therapy have hovered between 15 and 20%.[1,2] Because entecavir and tenofovir have nonoverlapping resistance patterns, an overhanging question has been whether combining these two potent agents might improve overall HBeAg or even HBsAg seroconversion rates. The study by Lok and colleagues does tell us, for the time being, that two drugs are not superior to one (in this study entecavir monotherapy was the competitor). The only possible exception would be those persons with high pretreatment HBV DNA levels; however, it should still be noted that despite the slightly higher rates of virologic suppression in this group, no differences in HBeAg and HBsAg seroconversion were observed. Thus, the combined use (and cost) of these two potent oral agents against HBV up front is not warranted, but individualized consideration using of two agents against HBV in high viral load patients may be considered.

One group of patients who have benefited from the evolution of nucleos(t)ide analog therapy has been those persons coinfected with HBV and HIV. Because of the dual activity of tenofovir (as well as emtricitabine) against both viruses, it is now recommended that persons with coinfection should receive treatment active against both viruses when therapy against either is warranted. The long-term use of tenofovir in coinfected persons has enabled us to glean important insights about long-term suppression and safety of this agent. The study by Lada et al tells us that a tenofovir-based regimen can produce highly successful outcomes in persons with HIV/HBV coinfection, whether patients are begun on tenofovir de novo or have it added because lamivudine-resistant HBV has developed. Concerns about renal toxicity (phosphate wasting, Fanconi syndrome) in HIV/HBV coinfected patients at higher risk for this adverse event were assuaged by the long-term data demonstrating preservation of GFR.

Although proportionally small, HBsAg loss can be observed in persons with HIV/HBV coinfection on long-term tenofovir-based therapy. The study by Zoutendijk and colleagues provides further correlates for HBsAg loss, and some of the strongest data yet for the utility of quantitative assessment of HBsAg levels. By indicating a threshold level below which most patients subsequently experience HBsAg loss, these data provide a potential tool for clinical decision making. (In another study presented at the conference but not reviewed here, Liu et al,[3] found a strong predictive value for HBsAg levels for spontaneous HBsAg clearance in a large cohort of prospectively followed HBV-infected persons in Taiwan.) That HBsAg quantitation can provide independent predictive value for HBsAg clearance suggests a potential surrogate target for future antiviral trials, whose efforts to surmount the plateau from suppression to clearance will be the next frontier of therapy.

Commentary References

1. Dienstag JL. Hepatitis B virus infection. *N Engl J Med.*2008;359(14):1486-1500.
2. Ayoub WS, Keeffe EB. Review article: current antiviral therapy of chronic hepatitis B. *Aliment Pharmacol Ther.* 2011;34(10):1145-1158.
3. Liu J, Lee M-H, Batrla-Utermann R, et al. Quantitative hepatitis B surface antigen levels are significant predictors of HBV DNA and HBsAg seroclearance in chronic hepatitis B. 62nd Annual Meeting of the American Association for the Study of Liver Disease. San Francisco, November 4-8. 2011. Abstract 239.

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HISTOLOGIC IMPROVEMENTS ASSOCIATED WITH LONG-TERM TREATMENT WITH TENOFOVIR FOR CHRONIC HBV INFECTION

Marcellin P, But M, Gane EJ, et al. Five Years of Treatment with Tenofovir df (TDF) for Chronic Hepatitis B (CHB) Infection is Associated with Sustained Viral Suppression and Significant Regression of Histological Fibrosis and Cirrhosis. 62nd Annual Meeting of the American Association for the Study of Liver Disease. San Francisco, November 4-8. 2011. Abstract 1375.

As many as 40% of untreated patients with chronic HBV infection will eventually develop cirrhosis, liver decompensation and hepatocellular carcinoma (HCC).[1,2] The goal of chronic hepatitis B treatment is to reduce histologic disease progression and prevent these serious, long-term sequelae of HBV infection. Since clinical outcomes of chronic HBV infection can emerge decades after infection, treatment goals and assessment of response rely on intermediate outcomes, principally diminishment of viral replication (i.e., HBV DNA levels), HBeAg seroconversion, loss of HBsAg, normalization of serum alanine aminotransferase (ALT) levels, and improvements in liver histology, including reduction or regression of fibrosis and cirrhotic disease.

A study presented at the 62nd Annual Meeting of the American Association for the Study of Liver Diseases demonstrated that anti-HBV therapy with tenofovir was not only associated with sustained virologic suppression (HBV DNA <400 copies/mL) over the long term, but that patients with chronic HBV infection who maintained virologic suppression for five years experienced significant improvements in liver histology, including reductions in fibrosis stage and reversal of cirrhosis.

Patrick Marcellin, of Hopital Beaujon in Clichy, France, and colleagues studied the impact of long-term tenofovir therapy on changes in liver fibrosis and cirrhosis in a large prospective cohort of patients who had sequential liver biopsies obtained at baseline and at one and five years following initiation of treatment. Study participants were originally enrolled in two large comparative trials of tenofovir and adefovir for the treatment of chronic HBV infection in HBeAg-negative (Study 102) and HBeAg-positive (Study 103) patients. In both studies, patients had the option to remain on or switch to open-label tenofovir after the 48-week randomized treatment period and undergo long-term follow-up. A total of 489 who chose to do so completed 240 weeks of follow-up on long-term tenofovir therapy; of these, a total of 348 patients had paired baseline and year 5 biopsies and were included in the histologic analyses.

Overall histologic improvement, defined as a reduction of two points or more in Knodell necroinflammation score with no worsening of Knodell fibrosis score, was observed in 88% of patients with paired baseline and year 5 biopsies. Looking at changes in Ishak fibrosis scores, the investigators found that 96% (335/348) of participants experienced either improvement (≥ 1 unit decrease in fibrosis score) or no worsening of fibrosis at year 5. Further, 71 of 96 (74%) of patients who entered the study with cirrhosis (baseline Ishak fibrosis score ≥ 5) were no longer cirrhotic at the study's end; all but one of these patients (n = 70) had decreases of ≥ 2 points in Ishak scores over the study period.

Significantly, this study had a very high retention rate; 84% of patients who entered the open-label phase remained on the study through five years. Fewer than 1.5% of patients discontinued tenofovir due to an adverse event, and renal events sometimes associated with tenofovir therapy were uncommon; only one patient discontinued for a mild creatinine elevation. Overall, 98% of patients on tenofovir remained virologically suppressed (HBV DNA < 400 copies/mL) through five years, and no resistance to tenofovir was detected during the study.

References

1. Lok AS. Chronic hepatitis B. *N Engl J Med.* 2002;346(22):1682-1683.
2. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med.* 2011;365(12):1118-1127.

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ADDITION OF TENOFOVIR TO ENTECAVIR FOR CHRONIC HEPATITIS B INFECTION SHOWS LIMITED BENEFITS

Lok AS, Trinh HN, Carosi G, et al. Entecavir (ETV) Monotherapy for 96 Weeks is Comparable to Combination Therapy with ETV Plus Tenofovir (TDF) in Nucleos(t)ide-Naive Patients with Chronic Hepatitis B (CHB): The BE-LOW Study. 62nd Annual Meeting of the American Association for the Study of Liver Disease. San Francisco, November 4-8. 2011. Abstract 223

Anna Lok, MD, of the University of Michigan Health System and colleagues presented the 96-week results from the BE–LOW study, comparing entecavir monotherapy (0.5 mg once daily) with entecavir (0.5 mg once daily) plus tenofovir (300 mg once daily) in 379 previously untreated adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease.

The investigators found no significant difference between the two treatment groups with respect to the primary efficacy endpoint of undetectable HBV viral load (HBV DNA <50 IU/mL or ~300 copies/mL). At 96 weeks 76.4% (139/182) and 83.2% (164/197) of participants in the monotherapy and dual therapy arm had achieved this endpoint, respectively (p = 0.0882).

Safety findings were also similar in the two treatment groups. Serious adverse events were reported in 6.6% and 7.1% of patients in the mono- and dual-therapy groups, respectively. A total of three deaths occurred during the study, all in the combination therapy group. Two patients in the entecavir monotherapy arm and five patients in the combination treatment arm discontinued treatment prior to week 96 (a criterion for treatment failure in primary analyses). Viral load rebounds were documented in two and seven patients in the entecavir and combination therapy groups, respectively; no evidence of genotypic resistance to either drug was observed in any case, however.

A small but statistically significant advantage was observed among HBeAg-positive patients treated with entecavir plus tenofovir relative to patients who received entecavir alone. Approximately 80% (111/138) of HBeAg-positive patients in the dual therapy arm achieved HBV DNA < 50 IU/mL compared to 70% (88/126) in the entecavir monotherapy arm (p = 0.0460). This difference was most pronounced among HBeAg-positive patients with high pretreatment viral loads (≥ 10^8 IU/mL), of whom 62% (49/79) in the monotherapy arm versus 78.8% (67/85) in the dual-therapy arm had undetectable HBV levels at 96 weeks. These results suggest a possible role for the combination of entecavir plus tenofovir for the treatment of HBeAg-positive patients with high baseline viral loads.

Subset analyses of HBeAg-negative participants demonstrated comparably high rates of viral suppression (~90%) in both treatment arms.

Secondary efficacy endpoints measured in the study included alanine aminotransferase (ALT) normalization, HBeAg seroconversion, and HBsAg loss. ALT normalization was observed in 81.9% (149/182) of participants in the monotherapy arm and 69% (136/197) in the dual-therapy arm. HBeAg seroconversion was observed in 32.5% (41/126) of patients who received entecavir alone versus 21.7% (30/138) of patients in the combination treatment group.

According to the findings of this study, the antiviral efficacy and safety of entecavir monotherapy is comparable, in general, with that of entecavir and tenofovir combined in nucleos(t)tide-naive adult patients with chronic hepatitis B with compensated liver disease. However, the combination of entecavir and tenofovir may be advantageous in treating HBeAg-positive patients with high pretreatment viral loads (HBV DNA ≥ 10^8 IU/mL).

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LONG-TERM TENOFOVIR FOR HIV/HBV COINFECTION

Lada O, Gervais A, Branger M, et al. Long-Term Efficacy and Safety of Tenofovir for Treatment of HIV/HBV-Coinfected Patients. 62nd Annual Meeting of the American Association for the Study of Liver Disease. San Francisco, November 4-8. 2011. Abstract 1428.

Zoutendijk R, Zaaijer HL, de Vries-Sluijs T, et al. Tenofovir Treatment for up to Eight Years Results in Pronounced HBsAg Decline in HBeAg-Positive HIV/HBV Co-infected patients. 62nd Annual Meeting of the American Association for the Study of Liver Disease. San Francisco, November 4-8. 2011. Abstract 1378.

The long-term safety and anti-HBV activity of tenofovir in patients coinfected with HIV/HBV were examined in two studies presented at the 62nd Annual Meeting of the American Association for the Study of Liver Diseases.

Olivier Lada and colleagues presented a retrospective study of the long-term efficacy and safety of tenofovir-containing therapy in HIV/HBV coinfected patients at Bichat Claude Bernard Hospital in Paris between 2003 and 2008. The investigators identified 61 patients with detectable HBV DNA (> 2.3 log IU/mL) at baseline who received initial antiretroviral therapy (ART) with tenofovir plus either lamivudine or entricitabine (Group 1; n = 15) or who added tenofovir to an ART regimen containing lamivudine (Group 2; n = 46). The median duration of tenofovir use was five years (range, three to seven years).

Approximately 90% of subjects all subjects were men; median age at enrollment was approximately 40 years. Subjects in the groups 1 and 2 had slightly different but comparable virologic characteristics at baseline, including median HBV DNA levels (6.1 vs. 6.5 log IU/mL), median HIV-1 RNA levels (<50 vs. 109 copy/mL), and median CD4 counts (381 versus 290 cells/μL); group 2 patients had a significantly higher rate of genotypic lamivudine resistance (6% vs. 41%, p = 0.03).

Study endpoints were initial and long-term viral suppression, HSsAg loss and HBeAG seroconversion, viral resistance, and safety surveillance including monitoring for renal toxicities and effects associated with use of tenofovir. The investigators reported that all tenofovir-treated patients had undetectable HBV DNA at the end of follow-up, and no evidence of virologic breakthrough was observed after primary viral suppression in any patient for a median off five years (range, three to seven years). Primary suppression of HBV DNA to undetectable levels was achieved by all group 1 patients within six months of treatment initiation and by 82% of group 2 patients within six months of adding tenofovir to ongoing lamivudine-containing antiretroviral therapy. An additional seven group 2 patients who were classified as adherent to therapy but also as primary nonresponders (< 1 log HBV DNA decline at month 6) experienced a delayed response to tenofovir and achieved undetectable HBV DNA levels after a median of 20 months (range, 17-24 months). HBeAg seroconversion occurred in 22% of the 37 study participants who were HBeAg-positive at baseline after a median duration of 12 months (range, 6-27 months) on tenofovir; HBsAg loss was documented in two patients after 18 and 23 months, respectively, of tenofovir treatment.

Fifty-four patients remained in follow-up through the last study visit, and all had undetectable HIV-1 RNA and HBV DNA levels with no evidence of virologic breakthrough throughout the observation period. Median alanine aminotransferase (ALT) levels declined in both treatment groups; 81% of all participants had persistently normal ALT measurements at last follow-up, and the remaining 10 patients had ALT levels below three times the upper limit of normal.

Tenofovir was well tolerated by all patients. No patients evidenced clinical changes in kidney function, and laboratory indices showed no evidence of renal impairment in this study population during a median duration of five years of tenofovir therapy. Median creatinine levels remained essentially unchanged between baseline (79 μmol/L; range, 66-117) and last follow-up (80 μmol/L; range, 61-128), and median estimated glomerular filtration rates (GFR-MDRD) and phosphatemia levels were within normal range at the end of the study period. The package label recommends carefully monitoring patients with preexisting renal insufficiencies who are receiving treatment with tenofovir. No such patients were included in this study.

Roeland Zoutendijk from Erasmus Medical Center in Rotterdam and colleagues studied HBsAg changes in 104 HIV/HBV coinfected patients treated with combination antiretroviral therapy (ART) containing tenofovir. Eighty-nine percent of patients were male, 57% were Caucasian, and 64% were HBeAg-positive. HBsAg levels were measured at baseline, six months, and then every year for a median duration of 56 months (range, 8-97 months).

The investigators found that HBeAg-positive patients had significantly higher HBsAg levels at baseline than did HBeAg-negative patients (median 4.6 vs. 2.8 log IU/mL; p <0.001), but they also experienced more robust and steady HBsAg responses to tenofovir-containing therapy over the course of the study. Twelve (18%) HBeAg-positive patients achieved HBeAg seroconversion, and five (8%) experienced HBsAg loss; three (8%) of HBeAg-negative patients also experienced HBsAg loss. Decreases in median HBsAg levels were greater and occurred more steadily in HBeAg-positive participants, with smaller improvements observed in HBeAg-negative patients. High baseline HBsAg levels were in fact associated with HBsAg decline in HBeAg-positive patients (p=0.035). Reductions in HBsAg levels seen in HBeAg-positive patients at months 6 and 12 were correlated with higher CD4 cell counts at these time points (p<0.05), suggesting a role for the effects of immune reconstitution in HBsAg clearance associated with ART in the context of HBV/HIV coinfection. Finally, the investigators reported that early changes in HBsAg kinetics in HBeAg-positive patients were predictive of HBsAg loss: HBeAg-positive patients with HBsAg levels <100 IU/mL at month 6 had a 71% probability of HBsAg loss, whereas none of the patients with HBsAg >100 IU/mL achieved HBsAg loss.

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