EDUCATIONAL HIGHLIGHTS FROM DATA PRESENTED AT THE

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## CHRONIC HEPATITIS B INFECTION: NAVIGATING THE ROAD TO SUCCESSFUL PATIENT OUTCOMES

**Historically, serologic monitoring has been used to identify chronic hepatitis B patients who are at risk for complications, and therapy has primarily been aimed at reducing the severity of the disease. However, recent studies demonstrate that serum levels of hepatitis B virus (HBV) DNA have an independent prognostic value. "As with any therapy in medicine, the primary goal of treating chronic hepatitis B is to improve outcomes. This goal can be reached through rapid and profound viral suppression, since there is a strong association of clinical outcome with HBV DNA levels. Suppressing the virus really makes a difference," said Douglas T. Dieterich (Division of Liver Diseases, Mount Sinai Medical Center, New York, NY, USA). Prof. Dieterich was one of the speakers at a satellite symposium that discussed critical questions with regard to the treatment of chronic hepatitis B, including the question of when to start, when to stop, and when to change therapy.**

### Early and sustained viral suppression improves outcome

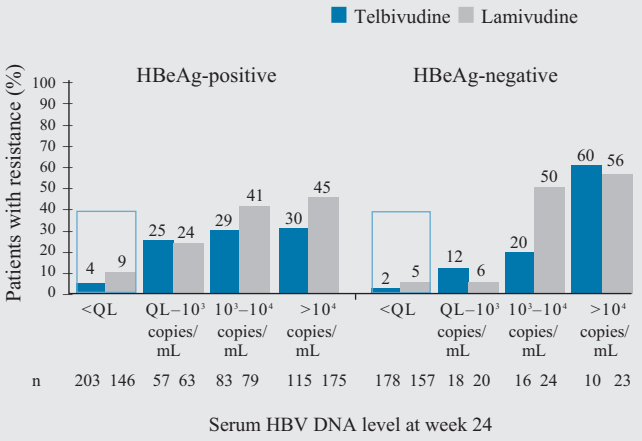
Natural-history studies have shown a direct correlation between histological necroinflammation of the liver and baseline viral load in untreated patients [1]. Importantly, high baseline HBV DNA is associated with a higher risk of progression to cirrhosis and hepatocellular carcinoma (HCC), as is demonstrated by the Risk Evaluation of Viraemia Elevation and Associated Liver disease study (REVEAL), a large prospective observational cohort study among 3,582 untreated Asian hepatitis B patients. A serum HBV DNA level of $\geq 10^4$ copies/mL came out as a strong independent risk predictor of cirrhosis [2] as well as of HCC [3], and the incidence of both types of complications significantly increased with further increasing HBV DNA levels. The highest HCC risk was found in subjects with elevated baseline serum HBV DNA that persisted over follow-up [3]. The increased incidence of cirrhosis and HCC with increasing viral load translates into a higher long-term risk of liver-related mortality, which explains the excess mortality in chronic hepatitis B patients compared to uninfected individuals [4].

A growing body of evidence supports early and sustained viral suppression as a way to prevent disease progression and improve survival in chronic hepatitis B. For example, in the randomised placebo-controlled Cirrhosis Asian Lamivudine Multicentre (CALM) study in patients with advanced fibrosis or cirrhosis, continuous treatment with lamivudine significantly decreased the time to complications, including hepatic decompensation and HCC. Virologic breakthrough during treatment, due to the emergence of lamivudine resistance, resulted in a higher progression rate compared to that in patients who did not become resistant [5]. This underscores the importance of preventing resistance to antiviral therapy, which is another advantage of early viral suppression that has been observed with several antiviral agents [6–9]. Prof. Dieterich: "The important thing to remember is that if you don't give the virus the opportunity to replicate in the presence of a drug, it will not develop resistance. The lower the HBV DNA level, the less resistance you will see." In addition, sustained suppression of HBV replication has been associated with increased rates of seroconversion, improved liver histology, and normalised alanine aminotransferase (ALT) levels.

The benefits of early viral inhibition to the lowest possible level are clearly illustrated by the GLOBE study, an ongoing randomised phase III trial of telbivudine versus lamivudine in 1,367 chronic HBV patients with compensated liver disease. The study's two-year results, which were presented at last year's AASLD meeting, confirmed the significantly greater antiviral and clinical efficacy of telbivudine versus lamivudine in hepatitis B e-antigen (HBeAg)-positive and HBeAg-negative patients. Moreover, patients receiving telbivudine demonstrated less primary-treatment failure and less viral breakthrough due to resistance. Very low rates of resistance were found in telbivudine-treated patients in whom HBV DNA was undetectable at week 24 (4% and 2% in HBeAg-positive and HBeAg-negative patients, respectively; Figure 1) [8]. A retrospective analysis of the two-year data presented at this

meeting revealed that the favourable efficacy and low resistance rate observed with telbivudine were predicted by low pretreatment HBV DNA (defined as $<10^9$ and $<10^7$ copies/mL in HBeAg-positive and -negative patients, respectively) and baseline ALT elevation, in combination with undetectable viral load at week 24. The strongest overall predictor of virologic and clinical outcomes after two years of therapy — including undetectable HBV DNA, absence of resistance, HBeAg seroconversion, and ALT normalisation — was viral load at week 24 [10]. A separate analysis of the one-year GLOBE data showed that on-treatment virologic suppression at week 24 by $\geq 10^5$ copies/mL significantly reduced the risk of histological progression. It suggests that using a more potent antiviral agent can result in histological improvements over periods as short as one year, the authors concluded [11].

Figure 1 **VIRAL RESISTANCE AT 2 YEARS IN RELATION TO ANTIVIRAL EFFECT AT WEEK 24**




QL = quantitation limit

*Source: Lai CL, et al. Hepatology 2006;44(Suppl. 1):222A (Abstr. 91).*

## The current HBV treatment landscape

Currently approved anti-HBV therapies include one immunomodulatory agent (peginterferon alfa-2a) and four nucleoside/nucleotide analogues (lamivudine, entecavir, telbivudine, and adefovir). Patrick Marcellin (Department of Hepatology, Hôpital Beaujon, Clichy, France) presented a concise overview of clinical results obtained with these drugs in chronic hepatitis B.

- Long-term follow-up data of HBeAg-negative patients who had been treated for 48 weeks with *peginterferon alfa-2a* demonstrate that ALT normalisation was sustained in one third of patients. In these patients HBV DNA was suppressed to approximately $10^4$ copies/mL or below, a level that is associated with a considerably reduced risk of complications and HCC. The number of patients with loss of hepatitis B surface antigen (HBsAg) increased over time to 8% at three years post treatment [12].
- HBeAg-positive patients who achieved a virologic response after two years of *entecavir* maintained virologic suppression to <300 copies/mL during a third year of therapy, with continued HBeAg loss and seroconversion [13].
- As already mentioned above, *telbivudine* was superior to *lamivudine* through a second year of therapy in HBeAg-positive and -negative patients. In the subset of HBeAg-positive patients with baseline ALT at least two times the upper limit of normal (ULN) — which reflects the population recommended for treatment in European, Asian, and American guidelines — the proportion of patients with undetectable HBV DNA was 61%, with a mean decline from baseline of almost 6 logs, while 72% had normal ALT. HBeAg loss and HBeAg seroconversion were observed in 41% and 36%, respectively (Figure 2). Resistance rates to telbivudine in the overall intent-to-treat population increased over time (to 21.6 and 8.6% in HBeAg-positive and HBeAg-negative patients, respectively), but remained significantly lower than with lamivudine [8].
- In a randomised head-to-head comparison of *telbivudine* versus *adefovir* in HBeAg-positive patients, telbivudine demonstrated greater and more consistent HBV DNA suppression than adefovir after 24 weeks of therapy. After one year, HBV DNA reduction was greater in patients who had continuously received telbivudine or were switched from adefovir to telbivudine after 24 weeks, compared to those who had been treated with continuous adefovir. Adefovir recipients with a suboptimal antiviral response at week 24 (HBV DNA level $\geq 10^3$ copies/mL) achieved a substantial incremental decrease in viral load after switching to telbivudine, suggesting that telbivudine is a useful rescue therapy in suboptimal responders and that treatment adaptation may be considered as early as week 24 [14].

Figure 2 **TELBIVUDINE VS. LAMIVUDINE (GLOBE STUDY): EFFICACY RESPONSES AT YEAR 2 (HBeAg-POSITIVE PATIENTS, BASELINE ALT ≥ 2 x ULN)**

**Population recommended for treatment in AASLD and APASL guidelines**
**Includes 66% of HBeAg-positive ITT population in GLOBE study**

| | Telbivudine | Lamivudine |
|---|---|---|
| n | 320 | 317 |
| HBV DNA ↓ from baseline (mean $\log_{10}$) | -5.8 | -4.8 |
| HBV DNA nondetectable by PCR (%) | 61 | 41 |
| ALT normalisation (%) | 72 | 63 |
| HBeAg loss (%) | 41 | 33 |
| HBeAg seroconversion (%) | 36 | 28 |

ALT = alanine aminotransferase; ITT = intent-to-treat; ULN = upper limit of normal;
AASLD = American Association for the Study of Liver Diseases;
APASL = Asian Pacific Association for the Study of the Liver

*Source: Lai CL, et al. Hepatology 2006;44(Suppl. 1):222A (Abstr. 91).*

## A roadmap to treatment success

The chronic hepatitis B guidelines issued by international societies address the natural history, diagnosis, and treatment of the disease, but do not focus on active management of patients once therapy is started. There is no clear consensus of these guidelines on how to use the available anti-HBV drugs in a way that maximises their therapeutic potential. Recently, a panel of

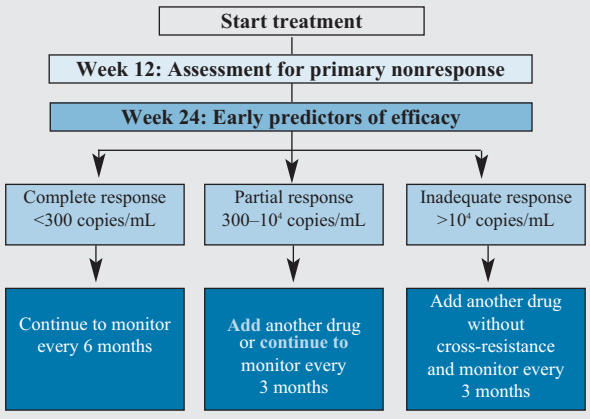
hepatology experts developed a 'road-map' for treatment of chronic hepatitis B that uses HBV DNA levels at specific time points (i.e., 12 and 24 weeks) as the basis for treatment adaptations. This should enable physicians to tailor their therapeutic strategy to the individual patient situation, with the aim of achieving higher response rates and better outcome [15]. Stefan Zeuzem (Internal Medicine 1, Johann Wolfgang Goethe-University, Frankfurt am Main, Germany) addressed some of the key considerations in this roadmap concept.

Treatment with nucleoside/nucleotide analogues offers various options, Prof. Zeuzem noted. "Any of these agents can be started as monotherapy. In clinical practice the initial monotherapy can often be maintained, especially in patients with low baseline viraemia. If there is an insufficient response, the patient can be switched to an alternative agent. However, there are good data to suggest that sequential monotherapy should be taken on with caution, because of the risk of resistance with long-term administration. Combination therapy, either as add-on or *de novo*, has therefore gained much attention.' The introduction of new, more potent antiviral drugs with a high genetic barrier to resistance will make *de-novo* combination therapy less important, he predicted. Nevertheless, it should be considered in patients with very high baseline HBV DNA levels, in those with advanced disease, and in immunocompromised patients (with the previous features combined).

Since many patients are on monotherapy currently, add-on combination treatment is a reasonable option. It has the additional advantage of being more cost effective than *de-novo* combination therapy. In a traditional add-on strategy, a noncross-resistant drug is added when, after initial response to the drug of first choice, the HBV DNA level starts to rise again. Early addition of the second drug — before the viral load has reached high levels and clinical signs of virologic breakthrough appear — significantly increases the chance of treatment success, as was for example demonstrated for adefovir in patients who have become resistant to lamivudine [16]. The roadmap concept proposes a modified add-on strategy in which a noncross-resistant drug is added if HBV DNA is not optimally suppressed at prespecified time points. According to this concept, patients with primary treatment failure at week 12 (defined as a <1 $\log_{10}$ drop in HBV DNA) require treatment adaptation, provided the suboptimal response is not due to noncompliance. Noncompliant patients can be kept on the initial therapy, but must be followed more closely and receive counselling.

The next stop on the roadmap is assessment of HBV DNA at week 24 (Figure 3). This time point was chosen based on the highly predictive value of viral load at week 24 for later outcomes at weeks 48 and 96, including suppression of HBV DNA and the likelihood of antiviral drug resistance [15]. Patients exhibit either a complete response (HBV DNA undetectable, which with the current tests means <300 copies/mL), a partial response (HBV DNA level 300–$10^4$ copies/mL), or an inadequate response (>$10^4$ copies/mL). In complete responders therapy can remain unchanged, but the patients should be retested every three to six months, depending on the stage of the disease and at the physician's discretion. The treatment decision in partial responders mainly depends on the selection of the initial monotherapy. In the case of a first-choice drug with a low genetic barrier to resistance, a second, more potent agent without evidence of cross-resistance must be added. Patients treated with a drug that has a low risk of resistance may be kept on therapy up to 48 weeks or beyond. However, monitoring HBV DNA at three-month intervals is mandatory, to see whether they become complete responders. If the viral load declines only slowly or reaches a plateau, treatment should be adapted. Finally, addition of a second, more potent drug is indicated in patients with an inadequate response at week 24, because these patients are at high risk for disease progression and the development of resistance. After treatment adaptation, HBV DNA must be assessed every three months, to monitor response to the combination therapy.

Figure 3 **MANAGEMENT ALGORITHM ACCORDING TO ON-TREATMENT RESPONSES**




*Source: Keeffe EB, et al. Clin Gastroenterol Hepatol 2007;5:890–897.*

Prof. Zeuzem once more emphasised that HBV DNA suppression early in the course of therapy is of paramount importance, as it minimises the risk of resistance. Maximal early and sustained viral suppression can modify the natural course of chronic hepatitis B and will prevent disease progression, he summarised. On-treatment management offers the greatest opportunity to achieve an optimal response to therapy; on the road to this goal, HBV DNA measurements are critical signposts. Close monitoring is strongly recommended for every patient, regardless of the drug that is administered.

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