

Overview of Therapy

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Substantial advances have been made in the treatment of hepatitis B in the past 10 years. In the United States, approved treatments for hepatitis B have increased from one to five (standard and pegylated interferon, lamivudine, adefovir, and entecavir) including three orally administered antiviral agents. The expanded treatment armamentarium has allowed a wider spectrum of patients, including those with decompensated cirrhosis, to be treated. The oral nucleoside analogs have negligible side effects and can be administered for many years. Studies using these new treatments have provided prospective data confirming that treatment of hepatitis B can lead to regression of hepatic fibrosis and prevention of liver disease progression.

Despite these advances, treatment of hepatitis B continues to be a challenge. The most effective means to prevent liver disease progression is to eradicate HBV, but this goal is not achievable. Thus, viral clearance is an impractical treatment endpoint, and withdrawal of treatment is usually accompanied by rapid viral rebound and at times severe hepatitis flares. Various surrogates have been used to assess treatment response. At the 2000 NIH Workshop, standardized definitions of response were proposed.¹ At that time, PCR assays for quantification of HBV DNA were not widely used, lamivudine was the only approved nucleoside analog, understanding of antiviral resistance was rudimentary, and the concept of primary nonresponse to treatment was not entertained.

Two key objectives of this 2006 meeting are to develop a consensus on definition of response and to standardize the format in which data from clinical trials should be presented. These will enable the safety and efficacy of various treatments to be compared. The ultimate goal is to provide practicing physicians with recommendations on who to treat, what should be the primary treatment, and when treatment can be stopped. A secondary goal is to identify areas that need further research.

The following section summarizes proposed definitions of response:

Responses to treatment can be assessed using biochemical, virologic, and histologic measures, and can be classified as initial, transient, sustained (off therapy), or maintained (during continued treatment). It must be emphasized that achievement of response is not necessarily an indication to stop treatment. For most patients with hepatitis B, the endpoints of treatment have not been established.

Biochemical response is generally defined as normalization of serum ALT levels. This is not applicable to patients who have normal ALT at baseline and may not be adequate for patients with cirrhosis. Biochemical breakthrough is defined as loss of response after initially achieving a biochemical response.

Virological response is defined based on changes in serum HBV DNA levels or HBV serological markers. A full virological response is defined as decrease of serum HBV DNA to levels that are

undetectable by a sensitive PCR-based assay (less than 60 IU/mL). A partial virological response can be defined as decrease of serum HBV DNA by at least 2 log₁₀ IU/mL and to less than 20,000 IU/mL. Clinical trials should report the percent of patients achieving full and partial virological response at specific time points in addition to median and interquartile log₁₀ IU reduction in HBV DNA levels. For patients who were initially HBeAg positive, virological response should include HBeAg loss. A complete virological response will include HBsAg loss. The proportion of patients with HBeAg loss, HBeAg seroconversion, and HBsAg loss at specific time points during and after treatment, and the number and percent of responders who reverted back to HBeAg positive after treatment withdrawal, should be reported.

It is now recognized that a small percent of patients receiving nucleoside analogs have minimal or no viral suppression. These patients are considered to have primary nonresponse, defined as < 2 log₁₀ IU decrease in serum HBV DNA after at least 24 weeks of treatment. Recent studies show that primary nonresponse is a strong predictor of antiviral resistance.

Virological breakthrough is defined as a reproducible increase in serum HBV DNA level of >1 log₁₀ IU/mL from a previous nadir during continuation of therapy. Reports of virological breakthrough in clinical trials should include all patients who meet the criteria above, not just patients who have virological rebound to high HBV DNA levels. Genotypic resistance should be performed on all patients who have detectable HBV DNA by PCR assays.

Histological response is generally defined as decrease in necroinflammatory score by at least 2 points with no worsening in fibrosis score. Histological response is rarely assessed in clinical practice. Furthermore, histological assessment can be subject to sampling error, and histological improvement during treatment may not be sustained when treatment is stopped or if antiviral resistance emerges.

The timing of assessment of response is critical. Clinical trials must specify whether response is assessed during or after treatment. Maintained response refers to persistence of response during continued treatment. Sustained or durable response refers to persistence of response after treatment is stopped. Relapse refers to loss of response after treatment is stopped.

Analyses should always be based on intention-to-treat. Reports on responses beyond the first year of treatment and off-treatment responses must clarify if the entire cohort is followed or if a subset of patients is reported and how the subset differs from the original cohort. Documentation of long-term safety, incremental responses during continued treatment, drug-resistance, and durability of response should be reported. Kaplan-Meier analysis and data on cumulative responses are inappropriate since responses may be lost due to antiviral resistance or treatment withdrawal. Responses should also be categorized according to baseline demographics, HBV DNA, HBV genotype, ALT, liver histology, and prior treatment.

Standardized reporting of data will improve understanding of available data and help to define questions that need further research. Some of the questions will include: Will HBeAg-positive patients with normal ALT benefit from currently available treatment? Can treatment be stopped in patients with HBeAg-negative chronic hepatitis? Will antiviral therapy prevent adverse clinical outcome? If so, which patients are most likely to benefit, what is the most appropriate

therapy, and how long should treatment be administered? Is there a role for monotherapy? If not, which combination is most appropriate? Can antiviral-resistant HBV be prevented? Can antiviral-resistant HBV be contained? How can multi drug-resistant HBV be prevented?

Reference

1. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000—summary of a workshop. *Gastroenterology* 2001; 120:1828-1853.