Liver Histology in Chronic Hepatitis B

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Liver disease in patients with hepatitis B infection represents an interaction between viral replication and the host immune response that attempts to eradicate the virus. The degree and the nature of the injury in any individual patient are determined by the balance between these two factors—how effectively the virus replicates and how vigorously and effectively the immune system reacts to the presence of the virus. Since hepatitis B is not directly cytopathic, it is the immune response that causes tissue damage in the liver, which over time may lead to scarring and eventually to cirrhosis and its complications. These processes are reflected in changes in liver histology that can be readily assessed in a liver biopsy.

Histologic features of chronic hepatitis B include:

1. Hepatocellular injury, characterized by apoptotic bodies and liver cell dropout.
2. Inflammation, predominantly lymphocytic, in the parenchyma at sites of liver cell dropout, in the portal areas, and most importantly at the interface between the parenchyma and portal connective tissue (interface hepatitis).
3. Repair of the damage with activation of Kupffer cells and hepatocellular regeneration.
4. Scarring with fibrous expansion of portal areas that can extend to link adjacent vascular structures (bridging fibrosis). As the disease progresses, the scarring can completely surround groups of liver cells and, along with hepatocellular regeneration, this produces the nodules of cirrhosis.

For most patients with chronic hepatitis B, the diagnosis is made on the basis of serologic and virologic testing. Liver biopsies are usually performed for grading and staging of the liver disease. The stage of any disease is a measure of how far it has progressed in its natural history, with the end stage resulting in death of the patient or failure of the organ; and so in chronic hepatitis B the end stage is cirrhosis with clinical decompensation, whereas earlier stages have lesser degrees of fibrosis or cirrhosis. The grade of a disease is meant to reflect how quickly the disease will progress to the end stage. In chronic hepatitis, it is thought that hepatocellular injury and inflammation, especially interface hepatitis, causes progression of fibrosis. Therefore, grading is an assessment of these features.

There are two major reasons for histologic grading and staging in chronic hepatitis B. First, and most often, histologic grading and staging are used in the management of individual patients, for prognosis, and as a guide to therapy. Secondly, improvement in liver histology can be used as an endpoint in clinical trials for new forms of therapy. These two functions of liver histology have different goals and therefore have different requirements and should use different methods for grading and staging. For management of an individual patient, the goal is that the grading of activity and staging of fibrosis be as accurate as possible in assessing the degree of inflammation and scarring in the liver. This requires an adequate size biopsy, preferably 2.5 cm or longer with a 16-gauge or wider needle, and a simple, reproducible staging and grading system. For clinical trials, the goal is to determine whether a cohort of patients treated with a new form of therapy shows significant improvement in histology when compared to a matched control cohort treated with placebo or a different therapy. In this case, statistical analysis and an adequate cohort size

can overcome some degree of sampling and interpretation variability, and so smaller biopsies and more complicated scoring systems can be used.

There are a number of systems in use for grading and staging of liver biopsies in chronic hepatitis, but the observations used for grading and staging are essentially the same no matter which system is employed. Periportal injury ("interface hepatitis" or "piecemeal necrosis"), lobular injury (apoptosis, "spotty necrosis"), and portal inflammation are all assessed as mild, moderate, or marked, and confluent (bridging or multilobular) necrosis is noted if present. In simple grading systems, an algorithm based on these observations is used to assign the grade, while in more complex systems, numbers are assigned for each feature, and the numbers are added. Staging the degree of fibrosis requires a connective tissue stain for proper evaluation. There is progression in stage of disease as the fibrosis advances from none to fibrous portal expansion to bridging fibrosis to incomplete cirrhosis and finally to established cirrhosis. Intermediate stages, such as early bridging fibrosis, marked bridging fibrosis, early cirrhosis, and advanced cirrhosis, can also be assigned and are used in some systems. Some widely used systems include:

1. Conventional verbal diagnoses—As revised by a special panel convened under the auspices of the International Association for the Study of the Liver (IASL), the severity of chronic hepatitis can be graded as minimal, mild, moderate, or marked, and the degree and location of fibrosis noted precisely.
2. Metavir—Activity has three grades and fibrosis has four stages.
3. Batts-Ludwig—Activity has four grades and fibrosis has four stages.
4. Scheuer—Scores added to give an activity of 0 to 8 and stage of 0 to 4.
5. Knodell—Scores added to give an activity of 0 to 18 and stage of 0, 1, 3, or 4.
6. Ishak—Scores added to give an activity of 0 to 18 and stage of 0 to 6.

The IASL conventional verbal diagnoses are the most appropriate grading and staging system for management of an individual patient, but Metavir and Batts-Ludwig can be used interchangeably with these by physicians who feel that a number is more scientific than a word. To assess whether liver histology has improved or worsened in followup biopsies from an individual patient, it is essential to look at both biopsies together, and it will be readily apparent if there has been improvement, worsening, or no significant change. Comparing biopsy reports or numbers on any scoring system is fraught with error.

For clinical trials employing large cohorts of patients, a wide range of values is better for statistical analysis. For activity, both Knodell and Ishak scores have a theoretical range of 0 to 18, although scores above 12 are rare in hepatitis B. The Ishak fibrosis score, with a range of 0 to 6 and no missing numbers, is better for assessing fibrosis. The data can be analyzed in many ways, although it is important to remember that the numbers correspond to categories rather than equidistant units. In using these scores as endpoints in early clinical trials, it was decided (negotiated between sponsoring companies and FDA) that a 2-point or greater decrease in the Knodell activity score was considered to be clinically significant "histologic improvement," and trials were evaluated by comparing the proportion of patients in each treatment cohort showing improvement. This standard fails to recognize the potential magnitude of improvement, and it ignores the fact that histology can worsen as well as improve. In more recent trials, improvement has been defined as a 2-point or greater decrease in inflammation with no worsening of the

Knodell fibrosis score; only a few patients are reclassified as treatment failures using the new definition. Nevertheless, with these definitions in the pivotal trials to gain FDA approval, both lamivudine and adefovir were significantly better than placebo, and entecavir was better than lamivudine in achieving "histologic improvement." Other ways of comparing the cohorts may be better in showing histologic improvement, and in fact, if an antiviral drug is truly effective in treating chronic hepatitis B, any way of comparing cohorts will demonstrate this with statistical significance. Other ways that have been suggested as standards for histologic improvement include: (1) change in mean or median activity score; (2) 50% decrease in activity score; (3) 2-point, mean or 50% improvement in Ishak rather than Knodell score; (4) 1-point improvement in Metavir score; (5) nearly normal liver biopsy defined as an activity score of 0 to 3. In the placebo controlled trials, patients on placebo were as likely to worsen as to improve histologically. Comparing the cohort on an active drug with one on placebo, the drug was better with high statistical significance in reducing mean and median activity scores (both Knodell and Ishak scores), in 1-point decrease in Metavir score, in 50% improvement in inflammation, and in the proportion of patients with nearly normal liver biopsies after treatment. Histologic improvement in inflammation is slower than virologic response, but nearly half of patients have little or no inflammation in liver biopsies after a year of effective antiviral therapy, and barring the development of drug-resistant mutants, improvement in both inflammation and fibrosis continues with prolonged treatment.

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