

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Noninvasive Markers of Liver Fibrosis

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### **G&H** What role does fibrosis monitoring play in the care of patients with chronic liver disease?

**NA** Standard-of-care practice, specifically for hepatitis C, is to utilize the stage of disease to guide treatment decision-making. Disease stage is determined by liver biopsy and the pathologist utilizes a scoring system such as the Metavir or Ishak systems to quantify the amount of fibrosis. We currently accept Metavir stages 0–1 as relatively mild fibrosis with only mild periportal scarring, whereas stages 2–4 range from septal fibrosis, through bridging fibrosis, to cirrhosis. Treatment is usually recommended for patients with stage 2–4 disease but clinical modifiers such as genotype may also affect treatment decisions.

Patients with favorable genotypes such as 2 and 3, for whom the course of treatment with interferon and ribavirin is shorter, often do not require biopsy, as treatment is generally recommended irrespective of the amount of liver disease. The other indications for biopsy monitoring are in the evaluation of chronic conditions, such as autoimmune hepatitis, primary biliary cirrhosis, and occasional diagnostic scenarios, when the cause of liver disease is unknown.

### **G&H** What are the concerns regarding liver biopsy as a tool for monitoring disease progression and staging?

**NA** Until recently, it was thought that biopsy had a very high reliability for staging disease. However, current studies suggest that disease is not as diffuse in the liver as originally thought, particularly in cases of hepatitis C and nonalcoholic steatohepatitis. There may be certain areas of the liver that are at stage 0, others at stage 1, and still oth-

ers at stage 2. A biopsy samples only 1/50,000 of the liver, which leaves a wide margin for sampling error. Sampling error can be as high as 30%, meaning that potentially 1 in 3 patients can be misstaged. Most of this misstaging is within one disease stage and it tends to occur in people who are at stages 1 or 2. Therefore, biopsy can create a sort of grey zone where patients can be staged incorrectly, leading to the potential for both over- and underutilization of treatment.

Several studies have been done where, in a single patient, biopsies are taken from both the right and left lobes of the liver and there is a one-stage difference in staging in almost 35% of cases. Another study correlated the findings of liver biopsy to the findings of laparoscopic examination, where the liver was actually visualized using a laparoscope at the site of the target biopsy. This study found that cirrhosis detected at the biopsy site laparoscopically was misdiagnosed by biopsy in 20% of cases. The idea that biopsy could fail to detect cirrhosis in 1 of 5 patients is cause for great concern.

Beyond all of these concerns regarding accuracy, it should be noted that the biopsy itself is invasive, expensive, and, in approximately 30% of patients, quite painful.

### **G&H** How are noninvasive markers being investigated and utilized to address the shortcomings of biopsy?

**NA** There are a tremendous number of markers and marker systems currently under investigation. Thus far, the perfect biomarker for the staging of liver fibrosis has not been discovered. There is no one marker that is 100% reliable and reproducible.

However, several tests utilizing panels of biomarkers to stage fibrosis have been validated and are currently available. The most widely utilized in the United States and worldwide is HCV Fibrosure (LabCorp). Fibrosure utilizes five different blood tests, also factoring in age and gender, to determine the patient's risk of fibrosis. The other panel commercially available in the United States, FIBROSpect (Prometheus Therapeutics and Diagnostics), utilizes three markers—hyaluronic acid, tissue-inhibited

metalloproteinase inhibitor (TIMP)-1, and  $\alpha$ -2 macroglobulin—which are considered to be more liver-specific than those utilized in the Fibrosure test.

### **G&H** How accurate are the noninvasive test panels in comparison to staging via biopsy?

**NA** Both of these tests provide a score on a linear scale. The scale is from 0 to 1 (Fibrosure) or from 0 to 100 (FIBROSpect). According to their score, patients are stratified as having mild (stage 0 or 1) or more advanced (stages 2–4) disease. At both ends of the spectrum, these tests are highly predictive. A patient scoring 0.1 or 10 (depending on the scale) has an extremely low chance of significant fibrosis and a 95% chance of having mild disease. This is the same as with staging via liver biopsy. If a patient scores 0.8 or 80, respectively, on these tests, then the likelihood for the presence of cirrhosis is 90–95%.

Approximately 50% of patients fall into these extreme ends. Those who fall in the midrange are classified with approximately 70% accuracy, which is again a similar rate to that achieved with liver biopsy. Overall, when analyzed via area under the receiver operating characteristics curve (AUC), these tests score about 0.85, which means that they are certainly as good as liver biopsy, which scores approximately 0.75.

### **G&H** Are there any other noninvasive methods for staging that utilize markers?

**NA** The commercial panels are the best-validated methods but there are other simple scoring systems that can be applied by the practicing clinician. These include formulas like the aspartate aminotransferase (AST)-to-platelet ratio index (APRI). This is a very simple scoring system, based on the fact that as AST levels rise with more and more advanced fibrosis, platelet levels go down. Utilizing the formula of AST over the control upper limit of normal, divided by platelet count (cells/ $\mu$ L), then multiplied by 100, a score above 1.0 is suggestive of fibrosis. APRI is an excellent auxiliary test because it can be calculated utilizing standard laboratory values that are measured in all patients as a matter of course.

Serum levels of hyaluronic acid, albumin, and AST (SHASTA) factor into another ratio for determining fibrosis from standard laboratory values. The specific utility of the SHASTA index is in staging coinfecting HIV patients. Each liver disease has different characteristics that affect the accuracy of testing and it is important to use the best test for each disease state.

In addition, it is always important to include age as a noninvasive factor, because the older the patient, the more likely the occurrence of fibrosis.

### **G&H** Can you describe the use of ultrasound as another noninvasive method?

**NA** Examining the physical properties of the organ itself is another method of evaluating liver fibrosis. Liver stiffness, which measures the extent that fibrosis has affected the elasticity of liver tissue, can be calculated via ultrasound, through a method recently developed by European clinicians.

Using a low-energy ultrasound probe, a 50 MHz ultrasound wave is passed into the liver and the velocity at which the wave moves through a 4–5 cm core of liver tissue is measured. The stiffer the liver tissue—that is, the more scar tissue that is present—the more rapidly the sound wave moves through it. One advantage of this method is that it enables the clinician to examine a larger area of liver than does biopsy. Whereas a biopsy examines 1/50,000, a stiffness measurement can examine 1/500 of the liver.

There have been studies correlating liver stiffness measures to liver histology. For the ability to differentiate mild-to-moderate disease, they have shown an AUC of approximately 0.88. For the diagnosis of cirrhosis, they are extremely effective, diagnosing cirrhosis correctly in 95% of patients. In addition, measures of liver stiffness are safe, easy, and quick to perform, requiring only about 5 minutes.

### **G&H** How should clinicians integrate these tests into their daily practice?

**NA** These tests can be used to screen patients for both significant and nonsignificant liver disease. I favor a combined approach of stiffness measurement and serum markers, which has been shown to be even more accurate than either modality alone. If patients score very low or very high, the likelihood of progression to liver disease is extremely low or extremely high, respectively. This information determines, in approximately 50% of patients, a diagnosis of either mild disease or advanced disease, thereby obviating the need for biopsy and allowing progression to other forms of observation and testing or treatment. The remainder of patients, who score in the midrange, can be followed with repeat testing or can be biopsied to confirm the marker findings. Even with the simple algorithms (APRI, SHASTA), biopsy could be avoided in over half the patient population.

### **G&H** Can you describe the potential cost savings with everyday use of these marker tests?

**NA** A biopsy costs, on average, \$2,000 with all of the expenses taken into consideration. The commercial

panels cost approximately \$400. APRI and SHASTA are free to calculate with values from basic blood work. The cost for liver stiffness is approximately €100 (\$128) per examination.

### G&H What future directions do you envision for research and utilization of these biomarkers?

**NA** Up to the present, these noninvasive markers have been utilized to measure the current extent of liver fibrosis. In the future, our hope is to be able to utilize them in order to predict the likelihood of liver disease progression and regression. Currently, there are data showing accuracy equal to that of biopsy in terms of prediction of clinical outcomes. Liver stiffness tests are also a fairly accurate predictor of portal pressure. The Fibrosure test has been shown to be as good a predictor of clinical outcomes as biopsy, suggesting that markers can accurately provide this kind of information. Other novel techniques in the fields of proteomics or proteoglycomics and gene testing may have a role to play but are less fully developed.

### Suggested Reading

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