ADVANCES IN HCV

Current Developments in the Management of Hepatitis C Virus Infection

FibroScan in the Diagnosis of Hepatitis C Virus Infection

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G&H Why is the evaluation of liver fibrosis important in the diagnosis and management of patients with hepatitis C virus infection?

NA The most important aspect in the evaluation of a patient with hepatitis C virus (HCV) infection is determining whether or not he or she has cirrhosis. This is the most important part of staging because very specific guidelines define how one should proceed with patients with cirrhosis in respect to screening them every 2–3 years for esophageal varices and portal hypertension and putting them into a program with cross-sectional imaging, ultrasound, computed tomography or magnetic resonance imaging (MRI) every 6–12 months for monitoring risk of liver cancer. It is very important that patients with cirrhosis who are at risk for liver cancer (which has an occurrence rate of 3–5% per year and is increasing) are identified and appropriately screened. All of these issues are independent of whether a patient is treated or cured because even patients who have a sustained viral response (SVR) remain at risk for cancer, which—although reduced—is still significant.

G&H What alternatives to liver biopsy are available to physicians in the United States, and why should alternatives be established?

NA The traditional method for staging liver fibrosis is biopsy; however, biopsy has 3 major drawbacks. One is sampling error, but even if adequately performed, biopsy has a 20% chance of undersampling the liver and returning an incorrect staging of the degree of cirrhosis. The second drawback is interobserver variability in staging, although variability is usually much more pronounced in intermediate stages of disease, and pathologists are usually pretty good at diagnosing cirrhosis. The third drawback to biopsy in the staging of liver disease is inadequacy of specimen size and fragmentation. An adequate biopsy should be nonfragmented, 2 cm in length, and contain at least 6, but preferably 10, portal tracts. Only 17% of biopsies in a large series from Dr. Thierry Poynard, Head of the Hepato-Gastroenterology Department, Groupe Hospitalier Pitié-Salpêtrière in Paris, France, met these criteria. Each clinician should be aware of the limitation of biopsy and evaluate these parameters to make sure that he or she believes that the biopsy findings accurately reflect the real stage of liver fibrosis.

In addition to these limitations, a small associated risk of significant complications, such as bleeding or pain, exists, and there is also the associated cost of the procedure and inconvenience to patients. In recent years, these drawbacks have led to a search for alternative ways to evaluate and stage the degree of liver fibrosis.

There currently are 2 alternative methods to stage liver fibrosis and a few other modalities that are under development. One available alternative is serum testing. Many serum tests are available. Some are simple and can be derived from standard biochemical tests. A perfect example of a serum test is the aspartate aminotransferase (AST) platelet ratio index (APRI) score, which is the AST over control divided by the platelet count. Patients with a high APRI score (>2) usually have significant scarring or cirrhosis. The problem with the APRI test is that it does

not identify disease until the disease is fairly advanced, and it is not a very good screening test for cirrhosis.

The 2 most widely used tests for liver fibrosis in the United States are the FibroSure (LabCorp) and HepaScore (Quest Diagnostics). Both tests are very good in terms of their sensitivity and specificity in diagnosing cirrhosis, but, similar to biopsy, they are not as accurate for exact identification of intermediate stages of disease. The scores are linear and a probability of patient disease stage can be inferred from the scores. In particular, patients who score above 0.75 on a scale of 0–1.0 have a significant likelihood of having cirrhosis. Test results are then confirmed using an elastography test, such as ultrasound elastography or magnetic resonance (MR)-based elastography. Ultrasound elastography includes FibroScan (Echosens and Sandhill Scientific). MR-based elastography is done using an MRI scanner. The advantages of ultrasound elastography are that it is easier to do, does not require an MRI, and can be done at the point of care. Specialists at the Beth Israel Deaconess Medical Center recommend using a combination of serum tests plus elastography to diagnose cirrhosis in lieu of liver biopsy. Either the serum test alone or the scan alone can be done, but it may be best to do both of them. If they have concordance about the presence of cirrhosis, then cirrhosis is highly likely. In discordant cases or where there is clinical suspicion of unreliability, the patient should undergo a liver biopsy. None of these tests replace liver biopsy, but they represent an alternative noninvasive modality to stage disease accurately.

G&H Which patients are the best candidates for FibroScan?

NA FibroScan can be performed in everybody. It is an incredibly simple, noninvasive test that takes 5 minutes to conduct. It could be done on every patient with HCV infection at the initial visit, and we find it very useful—not just for planning therapy—but in many cases, to alleviate patient fears of cirrhosis and advanced disease. It is also indicated to measure liver stiffness in other liver diseases since it is not dependent on the etiology of the liver disease. When the liver becomes scarred with fibrosis, it becomes stiffer. Organs that are stiffer will transmit a shear wave more rapidly than tissue that is soft. What is being measured is shear wave velocity—the speed at which a 50-mhz wave goes through the liver. From that, the liver's stiffness is calculated. The information can be used to help a clinician determine how much liver scarring has occurred.

G&H What are the limitations of FibroScan?

NA FibroScan cannot be performed in patients who have ascites, very tight intercostal spaces, or a large amount of subcutaneous fat around the chest wall, although there is a new probe, called the XL Probe (Echosens), that helps facilitate deeper penetration of the shear wave in patients with a lot of subcutaneous fat around the rib cage. Another limitation is false-positives, and clinicians need to keep in mind that conditions other than scarring can cause the liver to become stiff. These include significant inflammation, acute hepatitis, right heart failure with liver congestion, cholestasis, and jaundice of the liver.

G&H How is operator competence established?

NA The training is very simple and requires the performance of 50 or so procedures. The procedure is performed with the patient supine on his or her back, right arm above the head, and the images are taken through an intercostal space. Elastography is only accurate if more than 70% of the images are valid, 10 images are obtained, and the interquartile range is less than 30%. The median liver stiffness is then given, and the test can be deemed adequate. The interpretation is then made by the physician in relation to the clinical features of the patient. Information about the stage of fibrosis in a patient with HCV can then help the physician decide whether to immediately begin treatment or watch and wait. As treatments have improved, only liver cirrhosis appears to impact treatment outcome, with an associated reduction in SVR with both interferon-based and interferon-free treatments. This is an important issue because, as treatment becomes more tolerable and SVR rates continue to climb (approaching 90% for all genotypes), the need to know the exact stage of disease decreases, although the need to identify cirrhosis remains.

G&H What is the role of FibroScan in defining a treatment regimen for patients with HCV infection?

NA The treatment of HCV infection is changing all the time, and so as treatments get better, more patients are treated. The role of FibroScan is to help the clinician in staging the disease to determine whether treatment is more or less urgent. For example, patients with mild disease and a FibroScan stiffness score of less than 7 kPa can wait for new treatments, and there is less urgency to treat them immediately. However, disease stage is not the only determinant of treatment, and the choice of treatment is based on discussions between the patient and physician.

G&H What do you see for the future in regard to this technology?

NA I see it as a useful test for the evaluation of all patients with liver disease. The application is very similar to that of electrocardiograms and echocardiograms. The information

gained from FibroScan is so easily available and so rapid that it is worth performing in all suspected liver diseases. It may be a useful routine screening tool for use in other practices, beyond the specialties of gastroenterology and hepatology. For example, 30% of people in the United States have fatty liver disease. A critical decision regarding care of these patients is which should be referred to a specialist. A FibroScan will help in the decision-making process. If the patient scores high on it, that patient should be referred to a specialist. The impact of elastography on HCV infection will be a significant decrease in the need for liver biopsies, and, more importantly, we will see elastography used to refer more patients for appropriate therapy.

In addition, liver stiffness has recently been shown to be a good predictor of clinical outcomes over time. In a study performed at our institution in over 800 patients with all forms of liver disease, a stiffness score of less than 10 kPa was associated with a 99% chance of no adverse liver-related outcomes (cancer or decompensation) over a 3-year follow-up. Studies to understand what changes over time in relation to stiffness are also underway. In the future, patients may undergo annual elastography to assess and follow-up liver disease status. This is an exciting time for clinical investigation in assessing liver fibrosis, which can only benefit our patients in the future.

Dr. Afdhal has acted as a consultant/advisory board member for Echosens.

Suggested Reading

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