NASH IN FOCUS

Current Developments in the Management of Nonalcoholic Steatohepatitis

Section Editor: Stephen A. Harrison, MD

Role of Noninvasive Biomarkers in the Diagnosis of Nonalcoholic Steatohepatitis With Stage 2 or 3 Fibrosis

Rohit Loomba, MD, MHSc
Professor of Medicine
Director of Hepatology
Director of NAFLD Research Center
University of California at San Diego
La Jolla, California

G&H Why is the stage of fibrosis important in nonalcoholic steatohepatitis?

RL Patients with nonalcoholic fatty liver disease (NAFLD) can be divided into 2 broad categories. One category consists of patients with the nonprogressive form of NAFLD known as nonalcoholic fatty liver. These patients do not typically progress to cirrhosis or die from it, or their progression is extremely slow. The other category consists of patients with the progressive form of NAFLD known as nonalcoholic steatohepatitis (NASH). NASH can progress to fibrosis, cirrhosis, and hepatocellular carcinoma, and can result in liver-related mortality. In the NASH Clinical Research Network histologic scoring system, fibrosis is scored from 0 (no fibrosis), 1 (mild fibrosis), 2 (moderate fibrosis), 3 (bridging fibrosis) to 4 (cirrhosis). The stage of fibrosis is important because it is the greatest determinant of liver-related mortality among histologic features of NASH. Fibrosis is the sequela of NASH progression. As the progression increases, the stage of fibrosis increases.

It is also known that patients who have NASH with stage 2 fibrosis or higher have the greatest risk of progression and of dying from liver disease. A meta-analysis that my colleagues and I conducted in 2017 showed that stage 2 fibrosis or higher is the tipping point where the risk of liver-related mortality significantly increases. Therefore, it is these patients who need to be treated in the setting of a pharmacologic therapy. That is why the US Food and Drug Administration (FDA) requires patients to have NASH with stage 2 fibrosis or higher in order to be included in phase 3 trials for treatment response in NASH-related fibrosis.

G&H How has NASH with stage 2 or 3 fibrosis traditionally been diagnosed?

RL Traditional assessment and diagnosis is by liver histologic examination. Patients have to undergo liver biopsy. Features of steatohepatitis on liver biopsy are typically steatosis in zone 3 with lobular inflammation and ballooning or cellular injury with or without perisinusoidal fibrosis. Patients who have significant fibrosis are defined as those with stage 2 or higher.

G&H What are the challenges and limitations associated with this type of diagnosis?

RL There are approximately 80 million Americans and 1 billion people worldwide with NAFLD, but only 20% to 30% of these individuals have the progressive form known as NASH. Even among those patients, only approximately 50% have stage 2 fibrosis or higher. It would be impractical to subject 80 million Americans and 1 billion people worldwide to undergo liver biopsy in order to determine who has NASH with stage 2 fibrosis or higher. Therefore, noninvasive markers are needed to identify who should be left alone and who should be treated, especially with pharmacologic therapy for reversal of their liver disease.

G&H Which noninvasive biomarkers have been studied for the diagnosis of NASH with stage 2 or 3 fibrosis?

RL There are many biomarkers that are currently available. I am on the steering committee of NIMBLE (Non-Invasive Biomarkers of Metabolic Liver Disease),

a consortium between academics and stakeholders of the pharmaceutical and imaging industries that is funded by the Foundation for the National Institutes of Health and receives guidance from the FDA. One of the goals of NIMBLE is to noninvasively identify who needs to be treated in at-risk NASH (ie, patients who have NASH with stage 2 fibrosis or higher). We are taking biomarkers that are already being used in clinical practice to try to determine their diagnostic accuracy in a well-characterized, defined population of NASH patients; seeing if a combination of blood tests or biomarkers would be useful; and dividing biomarkers into clinical prediction rules. One example involves the Fibrosis-4 (FIB-4) score, which include the liver enzymes alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST), platelet count, and age. The FIB-4 score can be useful in ruling out advanced fibrosis (defined as stage 3 fibrosis or higher). Similar clinical prediction rules with different cutoffs can be used to rule out stage 2 fibrosis as well. The idea is to use, for example, the FIB-4 score to rule out patients who definitely do not need to be assessed, and then apply additional tests, such as an elastography-based method (eg, FibroScan or magnetic resonance [MR] elastography) to further risk stratify patients based upon a specific cutoff.

G&H Which other blood-based biomarkers have been considered?

RL Several serum biomarkers are currently being studied. One is the Enhanced Liver Fibrosis (ELF) panel, which can be used for the detection of stage 3 fibrosis or higher. For stage 2, a lower cutoff has to be used, and the diagnostic accuracy is not very high currently. Another test is FIBROSpect II, which has a diagnostic accuracy similar to that of the ELF panel for the detection of stage 3 fibrosis or higher. The fibrosis marker PRO-C3 has been considered, but its exact cutoff and role in the detection of NASH stage 2 fibrosis or higher has not yet been fully elucidated; studies are currently underway. A clinical test is also in development that combines ALT, AST, and a transient elastography–based test such as FibroScan or, where available, MR elastography to rule in patients who have stage 2 fibrosis or higher, but further research is necessary.

In addition, cytokeratin-18 fragments have been studied for the assessment of liver injury as a marker of apoptosis. This biomarker might be helpful in conjunction with other fibrosis-based markers, but not as a standalone marker. Lipidomic tests are also being developed; I have a patent for one such test. These tests need to be validated in larger studies before direct clinical application, but a combination approach may emerge in the next several years.

G&H Which are the main imaging biomarkers that have been studied in this setting?

RL The key imaging biomarkers involve elastography. FibroScan, or vibration-controlled transient elastography, can be used as a point-of-care test in a hepatologist's office. The typical cutoff used to rule out disease is much stronger than the cutoff to rule in disease. The cutoffs are not highly precise but are still clinically useful. Shear wave elastography, acoustic radiation force impulse imaging, and MR elastography have all been used to diagnose stage 2 or 3 fibrosis. Out of all of these imaging and serum biomarkers, MR elastography is the most accurate.

G&H Which of these biomarkers are currently being used most commonly in clinical practice thus far?

RL The biomarkers that are being used most commonly in clinical practice to look for the stage of fibrosis include FibroScan, MR elastography, shear wave elastography, and the FIB-4 score. These biomarkers are typically useful for excluding individuals with stage 3 fibrosis or higher. Patients can be excluded if they are below a certain value, but to include patients, a dual strategy is usually needed; one test is used to rule out patients and another test is used to rule in patients, although some may still need to undergo liver biopsy.

G&H Which of these biomarkers do you use?

RL Typically, I first use the FIB-4 score to exclude patients; with a score below 1, the likelihood of having stage 2 or 3 fibrosis is fairly low. Then, I might use FibroScan or MR elastography. If MR elastography has a value of 3 kPa or higher, the likelihood of having NASH with stage 2 fibrosis or higher is approximately 85%. I typically consider such patients for liver biopsy. A value of 3.63 kPa or higher indicates stage 3 fibrosis or higher, with an accuracy of approximately 92%.

The NAFLD fibrosis score is also an option, but I typically end up using the FIB-4 score instead because it is easier, probably more informative, and more accurate, in my opinion.

G&H How has your experience been using these noninvasive biomarkers?

RL Understanding the caveats associated with them is important, as is knowing the true negative and positive predictive values. Thus, in the right context, noninvasive biomarkers can be very useful and can help stratify patients. I also use them to monitor patients because

biopsies cannot be repeated very often. My colleagues and I recently published an article in which a 15% increase in MR elastography was associated with high odds of fibrosis progression. Such a patient should likely be brought back for a biopsy. If the patient does not have that much of an increase, he or she does not need repeat clinical evaluation or a change in management.

G&H Do you think that the use of noninvasive biomarkers will become more widespread and eventually replace liver biopsy?

RL Their use is already becoming more and more widespread. I expect that once new therapies become available and approved by the FDA—with the first drug, obeticholic acid (Ocaliva, Intercept Pharmaceuticals) likely to be approved this year—these biomarkers will become even more important, leading to greater utility and utilization and, subsequently, less need for liver biopsy. I do not think that the biomarkers will completely replace or eliminate liver biopsy, but the number of patients needing this procedure will significantly decrease.

G&H Could you expand on the significance of noninvasive biomarkers with the upcoming approval of treatment targeting NASH patients with stage 2 or 3 fibrosis?

RL It is important to be able to reliably diagnose patients (eg, with 90% accuracy) with NASH and stage 2 fibrosis or higher so that they can be treated and to reliably exclude patients who have cirrhosis without needing a biopsy. We may be able to come up with a window in which patients with a FIB-4 score below 1 can be excluded and do not need to be treated. Patients with a FIB-4 score above 1 may have to undergo testing for an ELF panel. Patients who have a score above 9.8 and have a certain FibroScan or MR elastography value may then be qualified for treatment without needing a liver biopsy. Of course, there may be some patients who are in gray zones or discordant between FibroScan and an ELF panel who may need to undergo liver biopsy. I think that is how noninvasive testing will play out over the next several years once new therapies become available.

G&H Why is pharmacologic therapy so important at these stages of fibrosis?

RL If the disease is not reversed, the patient has a very high risk of dying. Lifestyle interventions can be effective at reversing NASH and are the first choice, but the uptake of this approach and the ability to sustain it is currently dismal. Therefore, pharmacologic therapy is needed to prevent progression to cirrhosis and mortality due to liver disease.

G&H What are the next steps in research in this area?

RL One of the next steps is to identify the ideal combination of noninvasive biomarkers to see who needs to be treated and who would be safe for that treatment. When treatment is started, it would be useful to be able to use another noninvasive biomarker to determine whether the patient is responding to treatment or if the patient is a nonresponder, in which case another drug might be considered. Another next step might be to use precision medicine to identify which patients should be treated with which types of drugs.

In addition, if patients are followed noninvasively, we need to define what percentage of an increase in a noninvasive test is associated with a high risk for liver-related mortality and what percentage of a decrease is associated with improved liver-related survival.

Dr Loomba serves as a consultant or advisory board member for Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Cirius, CohBar, Galmed, Gemphire, Gilead, Glympse Bio, GNI, GRI Bio, Intercept, Ionis, Merck, Metacrine, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Siemens, and Viking Therapeutics. In addition, his institution has received grant support from Allergan, Boehringer Ingelheim, Bristol-Myers Squibb, Cirius, Eli Lilly and Company, Galectin Therapeutics, Galmed, GE, Genfit, Gilead, Grail, Intercept, Janssen, Madrigal Pharmaceuticals, NGM Biopharmaceuticals, Pfizer, pH Pharma, Prometheus, and Siemens. He is also cofounder of Liponexus, Inc.

Suggested Reading

Ajmera VH, Liu A, Singh S, et al. Clinical utility of an increase in magnetic resonance elastography in predicting fibrosis progression in nonalcoholic fatty liver disease [published online September 25, 2019]. *Hepatology*. doi:10.1002/hep.30974.

Arulanandan A, Loomba R. Non-invasive testing for NASH and NASH with advanced fibrosis: are we there yet? *Curr Hepatol Rep*. 2015;14(2):109-118.

Balakrishnan M, Loomba R. The role of noninvasive tests for differentiating NASH from NAFL and diagnosing advanced fibrosis among patients with NAFLD. *J Clin Gastroenterol*. 2020;54(2):107-113.

Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;156(5):1264-1281.e4.

Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328-357.

Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. *Hepatology*. 2017;65(5):1557-1565.