NASH IN FOCUS

Current Developments in the Management of Nonalcoholic Steatohepatitis

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Magnetic Resonance Elastography as a Predictor of Response to Therapy in Patients With Nonalcoholic Steatohepatitis

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G&H How is response to therapy defined in patients with nonalcoholic steatohepatitis?

MN Approximately 5 years ago, experts, regulators, and governing societies sought to determine the best primary efficacy endpoints for treatment response in nonalcoholic steatohepatitis (NASH) clinical trials. At that point, it was determined that fibrosis improvement by 1 stage without worsening of NASH can be used as a primary endpoint for registry trials. This was based on data showing that patients with fibrosis, particularly stage 2 and higher, have worse outcomes. In addition, because NASH is the driver of underlying disease pathogenesis, another efficacy endpoint that can be used is NASH resolution without worsening of fibrosis. Thus, 2 primary endpoints were established for NASH clinical trials and are used mainly for patients with NASH stage 2 and 3 fibrosis. For cirrhosis, the endpoint that is mostly used is improvement by 1 stage of fibrosis or looking at hard outcomes; however, the latter might take a longer time to achieve, particularly if patients are enrolled early on in the process with compensated cirrhosis. This is how response has been defined recently, but there have been promising advances in the field of noninvasive testing that have been used mainly in phase 2A and less commonly in 2B trials, which are performed earlier than registry trials.

G&H What is the utility of magnetic resonance elastography in this setting?

MN The natural progression of the study of biomarkers such as magnetic resonance (MR) elastography starts with cross-sectional study, then longitudinal study (which typically correlates with histology), and eventually correlation with outcomes (which takes longer). During a conversation, Dr Theo Heller from the National Institutes of Health and I coined the helpful term SLO (which stands for staging, longitudinal, and outcomes) for biomarkers. Staging data from Dr Rohit Loomba's group at the University of California San Diego have shown the utility of MR elastography, with the modality demonstrating high accuracy in correlating F0 to F4 with histologic stages. My colleagues and I recently conducted a cross-sectional study that showed that the higher the liver stiffness, the greater the likelihood of clinical liver events. The cutoff of 6.4 kPa was associated with a high likelihood of decompensation and can be used as an endpoint for decompensation in clinical trials. We also found that an increase of liver stiffness by 1 kPa resulted in an increase of decompensation by an odds ratio of approximately 3. Dr Alina Allen and colleagues at the Mayo Clinic followed patients for several years and showed in a retrospective analysis that increased liver stiffness led to decompensation by a hazard ratio of approximately 1.32. They also showed that baseline liver stiffness on MR elastography predicted future cirrhosis. Thus, data are now connecting MR elastography with clinical outcomes.

G&H How accurate does MR elastography appear to be as a predictor of treatment response in NASH clinical trials?

MN Data are now emerging on the accuracy of MR elastography in terms of predicting response in clinical

trials. My colleagues and I recently developed the MAST score, which combines MR elastography, MR imaging proton density fat fraction (MRI-PDFF), and aspartate aminotransferase, to predict response in patients with NASH who have a Nonalcoholic Fatty Liver Disease Activity Score of 4 or higher and a fibrosis stage of 2 or higher. We applied this score to data from resmetirom (MGL-3196, Madrigal) studies and showed that the score moved in response to treatment in the resmetirom arm compared with the placebo arm. We are presenting these data at the next meeting of the American Association for the Study of Liver Diseases (AASLD). In addition, post hoc data from the aforementioned resmetirom studies, presented at a previous AASLD meeting, showed that MR elastography improved with the use of resmetirom. However, more data are needed correlating improvement on MR elastography with histology. We also need to show that improvement in histology correlates with improvement on MR elastography in particular in the treatment arm. Overall, data regarding the correlation of MR elastography with outcomes have certainly shown promise.

G&H Could you further discuss recent data demonstrating a link between MR elastography and outcomes, particularly in patients with NASH who have cirrhosis?

MN In the aforementioned recent cross-sectional study, my colleagues and I performed a multicenter retrospective study of 320 patients with nonalcoholic fatty liver disease who underwent MR elastography. We sought to examine the cutoffs that correlated with clinical liver events (defined as decompensation events and death). Patients were grouped based on whether they had compensated cirrhosis, decompensated cirrhosis, or no cirrhosis. For differentiating cirrhosis from noncirrhosis, the best cutoff was 4.39 kPa, whereas for distinguishing compensated cirrhosis from decompensated cirrhosis, it was 6.48 kPa. As mentioned, the likelihood of decompensation rose as liver stiffness increased. An increase in liver stiffness was also associated with ascites, hepatic encephalopathy, esophageal variceal bleeding, and mortality.

G&H How do these data compare with data on other tools, such as serum biomarkers or transient elastography?

MN The best serum biomarker comparison to MR elastography is the Enhanced Liver Fibrosis (ELF) score. A baseline ELF score of approximately 9.3 is predictive of progression of cirrhosis, and a baseline ELF score of 11.7 is predictive of decompensation of cirrhosis. In terms of imaging, data on transient elastography (FibroScan, Echosens) from Dr Jérôme Boursier and colleagues showed that an increase in liver stiffness on transient elastography correlated with clinical liver outcomes. Data recently published in *Clinical Gastroenterology and Hepatology* showed that an increase in liver stiffness of 20% correlated with increased clinical liver events, including decompensation, whereas a decrease of 20% correlated with fewer clinical liver events. Thus far, the top 3 biomarkers that show correlation with outcomes overall are the ELF score, MR elastography, and transient elastography.

G&H How does MR elastography compare directly with transient elastography and the ELF score?

MN Data comparing MR elastography with transient elastography have shown that MR elastography is superior in terms of the assessment of each stage of fibrosis. MR elastography has also been shown to be superior to the ELF score in terms of fibrosis staging and is more granular in terms of fibrosis assessment than the ELF score. Therefore, MR elastography is one of the most accurate biomarkers for assessing fibrosis stages when compared with other biomarkers. However, it is one of the least utilized, given its availability around the world, although its use has been increasing over the last several years.

G&H Are there any other advantages to using MR elastography in patients with NASH?

MN Another advantage of MR elastography is that it can be used in obese or severely obese patients, which is particularly important in NASH because obesity is prevalent. Although transient elastography has improved its capability for use in obese patients, an XL probe is needed and this modality still has some limitations in morbidly obese patients.

G&H What are the main limitations or challenges associated with using MR elastography in patients with NASH?

MN The main limitations involve cost, availability, and expertise. However, the last 2 of these have been less of an issue with adequate training and the increasing use of MR around the world.

G&H Should MR elastography be used in combination with other imaging tools to predict treatment response in patients with NASH, particularly those with cirrhosis?

MN I would. When patients with NASH reach cirrhosis, most start losing fat in the liver but some continue to have it. However, whether or not patients continue to have liver fat, using MRI-PDFF at the same time as MR elastography would be helpful.

NASH patients with cirrhosis usually continue to have an inflammatory signal, so clinicians can also use a corrected T1 (cT1) via multiparametric MR imaging. Therefore, when measuring stiffness, changes in inflammatory signal are also measured. In the latter stages of cirrhosis, patients may lose both fat and the inflammatory signal, resulting in what is called burnout (or cryptogenic) cirrhosis, which has been defined by my colleagues and I from the Liver Forum NASH Cirrhosis Working Group. At that point, stiffness on MR elastography can be measured alone.

G&H Which of these noninvasive imaging tools do you typically use in patients with NASH who have cirrhosis?

MN In my clinic, MR imaging is customized to have both MR elastography and MRI-PDFF. In addition, we recently added cT1 so that all 3 of these are used together. I also have transient elastography in my office, and because I am at a research center, all of these tools are used together at the same time. The decision to perform liver biopsy in patients with cirrhosis is usually based on a research protocol.

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

MN This exciting area of research is currently wide open. As mentioned, in terms of noninvasive testing, more data are needed to show that MR elastography improvement can correlate with histologic improvement. Currently, we have data showing that MR elastography worsening leads to worsening of outcomes, but we need to show that MR elastography improvement leads to improvement in outcomes. As for patients with cirrhosis, which are a much more difficult population to treat, we need to show that we can regress fibrosis. At the last meeting of the European Association for the Study of the Liver, Dr Stephen A. Harrison presented results from a small study showing regression in histology in cirrhotic patients using efruxifermin compared with placebo. A larger sample size and a longer duration of follow-up are needed using this agent. It would be helpful if we could combine such a study with MR elastography and show that the histologic regression in patients with cirrhosis correlates with improvement in stiffness on MR elastography.

Disclosures

Dr Noureddin has been on the advisory board for 89bio, Gilead, Intercept, Pfizer, Novo Nordisk, Blade, Echosens, Fractyl, Terns, Siemens, and Roche Diagnostics; has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking, and Zydus; and is a minor shareholder or has stocks in Anaetos, Rivus Pharmaceuticals, and Viking.

Suggested Reading

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