MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

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Overview of Metabolic Dysfunction-Associated Steatohepatitis Cirrhosis

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G&H Which patients with metabolic dysfunction-associated steatohepatitis are at greatest risk of progressing to cirrhosis, and how often does this occur?

MN The patients at greatest risk are those who have advanced fibrosis (F3) but do not have cirrhosis yet. One study found that approximately 20% of patients with metabolic dysfunction-associated steatohepatitis (MASH) and advanced fibrosis will progress to cirrhosis within 2 years. Additionally, patients with type 2 diabetes and MASH are more likely to progress to cirrhosis than nondiabetic patients, carrying a 2- to 3-fold higher risk of progression to advanced fibrosis and cirrhosis. Thus, roughly 15% to 20% of patients with MASH and diabetes progress to cirrhosis over 10 to 20 years vs 5% to 10% of those without type 2 diabetes.

G&H What are the most common outcomes of MASH cirrhosis?

MN It is silent at the beginning, but patients can eventually develop ascites, variceal bleeding, and hepatic encephalopathy after developing portal hypertension. In addition, patients with MASH cirrhosis have an increased risk of hepatocellular carcinoma. Those complications can be deadly and can eventually lead to decompensation and the need for liver transplantation.

G&H Which noninvasive tests can be used for the evaluation of MASH cirrhosis?

MN A number of noninvasive tests are currently available, but the most commonly used ones are transient elastography and magnetic resonance (MR) elastography. If a certain value is attained, providers can tell that a patient is cirrhotic. There are other noninvasive tests as well, such as blood-based tests. One example is the Enhanced Liver Fibrosis test, which analyzes 3 biomarkers to calculate a risk score for liver disease progression, including cirrhosis. Providers can also use these noninvasive tests in combination (eg, imaging + a blood test). In terms of accuracy, MR elastography is the most accurate test, followed by transient elastography and then blood tests. Using tests in combination increases accuracy to as good as, if not better, than liver biopsy.

G&H Is liver biopsy still needed in this setting?

MN It is possible to get away from using liver biopsy in this clinical setting. There are other well-known clinical parameters, such as nodular liver, evidence of portal hypertension, lower platelet count, and thrombocytopenia, that can be combined to help identify the presence of cirrhosis. The aforementioned noninvasive tests can tell providers even earlier whether a patient is cirrhotic.

G&H What are the main challenges of drug development and clinical trial design for MASH cirrhosis?

MN There are several challenges. One is whether the drug will be effective in patients with cirrhosis and in which stage. Some patients have early cirrhosis, others have more advanced cirrhosis with clinically significant portal hypertension, and, beyond that, still others have decompensation. The biggest question is whether a drug will be effective in all those subgroups. Another challenge is

whether liver biopsies are needed. Many trials still require them or follow patients to certain outcomes, which can be the point of no return. Examples include ascites, hepatic encephalopathy, and variceal bleeding. Additionally, these outcomes can take a relatively long time overall.

G&H What research has been presented thus far on the use of resmetirom in patients with MASH cirrhosis?

MN Resmetirom (Rezdiffra, Madrigal) was approved last year by the US Food and Drug Administration for the treatment of MASH patients who do not have cirrhosis. At this year's meeting of the European Association for the Study of the Liver, results were presented from a single-arm open-label trial of patients with MASH cirrhosis who were identified using noninvasive testing such as the Baveno VI criteria as well as the modified Baveno VI criteria, which use a combination of vibration-controlled transient elastography (VCTE) results and platelet count. Despite the lack of a placebo arm, an improvement in clinically significant portal hypertension (measured via VCTE and platelet count) was seen in patients with MASH cirrhosis receiving resmetirom, which is encouraging. The randomized controlled MAESTRO-NASH-OUTCOMES trial is still ongoing and will hopefully report in 2027 or 2028 whether resmetirom is able to reverse cirrhosis or portal hypertension.

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G&H Have fibroblast growth factor 21 agonists shown any promise for the treatment of patients with MASH cirrhosis?

MN Results of a randomized placebo-controlled trial were recently published in *The New England Journal of Medicine* in which patients with MASH and biopsy-confirmed compensated cirrhosis received efruxifermin and underwent liver biopsy at week 36 and week 96. The primary endpoint of regression of fibrosis on biopsy at week 36 was not met. Nevertheless, the trial continued for the second biopsy at week 96, and reversibility of fibrosis was seen in approximately one-quarter of patients on paired analysis and in up to 17% of patients on intention-to-treat analysis. This trial was the first to show reversibility of fibrosis in patients with MASH cirrhosis. That occurred at week 96, but it makes sense that the longer the duration, the more likely that the drug would work.

There have also been some small phase 2 trials of other fibroblast growth factor 21 agonists in MASH patients with F2 and F3 fibrosis that included a few cirrhotic patients. Further research is needed in larger studies.

G&H What research has been conducted thus far on the use of glucagon-like peptide-1 receptor agonists in patients who have MASH cirrhosis?

MN There have been several efforts looking at this therapeutic approach. The most striking involves the use of semaglutide in a randomized placebo-controlled trial of patients with well-compensated cirrhosis identified by liver biopsy. Unfortunately, that trial had negative findings. A phase 3 trial of survodutide is currently underway in patients who have MASH cirrhosis. Early phase 1b data from a hepatic impairment trial showed improvement using noninvasive testing such as MR elastography and other fibrosis biomarkers with this drug. Thus, survodutide is the glucagon-like peptide-1 receptor agonist in the most advanced stage of investigation in cirrhosis trials. Pemvidutide recently announced positive data on its use in patients with MASH F2 to F3 fibrosis and is expected to undergo a phase 3 study in cirrhotic patients.

G&H Are any other studies currently underway for the treatment of patients with MASH cirrhosis?

MN There is an ongoing phase 2 trial on efimosfermin in MASH cirrhotic patients, and the results are being eagerly awaited. Additionally, the Galectin-3 trial showed prevention of progression to varices, as has been shown in the past, with the medium dose of belapectin. However, it is unclear whether this drug will continue phase 3 development at this point. Because of regulatory requirements for inclusion of MASH cirrhosis trials, there are other medications that will likely be tapped for MASH cirrhotics.

G&H What are the priorities of research regarding MASH cirrhosis?

MN The ultimate goal is having a drug that is efficacious and can reverse clinically significant portal hypertension, and promising results are starting to be seen. Data on clinically significant portal hypertension are expected to be presented from the aforementioned efruxifermin trial that was recently published in *The New England Journal of Medicine*. Additionally, the field is still looking for primary endpoints involving noninvasive testing that are easier to use than outcomes, and is trying to avoid liver biopsies. Finally, research is needed on combination therapy in patients with MASH cirrhosis. I would expect this therapeutic approach to be more efficacious than monotherapy. Results from a trial that combined semaglutide, cilofexor, and firsocostat will be presented at the upcoming American Association for the Study of Liver Diseases meeting.

> There is a notion that cirrhosis is irreversible, and that is simply not true.

G&H Are there any misconceptions in this area that you would like to clear up?

MN There is a notion that cirrhosis is irreversible, and that is simply not true. We have seen this in hepatitis B data, as well as hepatitis C data, and, as I have mentioned, more recently in the efruxifermin cirrhosis trial in which reversibility of fibrosis was seen in patients with cirrhosis. The reversibility of cirrhosis is a very important concept.

Additionally, a lot of people do not realize that there are ongoing trials on patients with cirrhosis. As I have mentioned, there are multiple trials currently underway, so providers should be on the lookout for these findings to offer patients with cirrhosis options.

Disclosures

Dr Noureddin has served on the advisory board/has consulted for Akero, Aligos, Altimmune, AstraZeneca, BI, Boston Pharmaceuticals, Curve Biosciences, CytoDyn, GSK, Histoindex, Lilly, Madrigal, Merck, Novo Nordisk, Rivus, Sagimet, Takeda, and Terns; has served as principal investigator for a drug study for Akero, Allergan, Altimmune, BI, BMS, Boston Pharmaceuticals, Conatus, Corcept, Enanta, Galectin, Genfit, Gilead, GSK, Kowa, Lilly, Madrigal, Merck, Novartis, Novo Nordisk, Rivus, Shire, Takeda, Terns, Viking, and Zydus; has been a stockholder of Akero and Rivus; and has served on the speakers bureau for Madrigal and Novo Nordisk.

Suggested Reading

Aggarwal P, Noureddin M, Harrison S, Jeannin S, Alkhouri N. Nonalcoholic steatohepatitis (NASH) cirrhosis: a snapshot of therapeutic agents in clinical development and the optimal design for clinical trials. *Expert Opin Investig Drugs*. 2022;31(2):163-172.

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