MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

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Update on Treatment for Metabolic Dysfunction-Associated Steatohepatitis Cirrhosis

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G&H What is the likelihood that a patient with metabolic dysfunction-associated steatohepatitis has cirrhosis?

WA The likelihood of cirrhosis depends on which patients with metabolic dysfunction-associated steatohepatitis (MASH) are being considered and their individual risk factors. For example, patients with MASH and type 2 diabetes are at greater risk of developing advanced fibrosis or cirrhosis than those without diabetes. Other risk factors include cardiometabolic conditions (such as hypertension, hypercholesterolemia, and obesity), genetic predisposition, and diet. Certain ethnic groups are also at heightened risk, and socioeconomic factors such as deprivation are important as well.

Patients who have progressed to cirrhosis are at increased risk of developing hepatocellular carcinoma and liver failure; hence, this is the point at which surveillance and more intensive monitoring kick in.

However, perhaps the biggest challenge to identifying patients with cirrhosis is that providers do not assess for fibrosis in all patients at risk for MASH. In clinical practice, patients with cirrhosis are likely identified using a series of noninvasive tests that first rule out significant fibrosis with a good negative predictive value, followed by a second test to help identify those patients who are likely to have advanced fibrosis or cirrhosis or those who would benefit from a liver biopsy. Such algorithms and pathways have significantly reduced the number of patients who need to have a liver biopsy to determine the stage of fibrosis or diagnose cirrhosis. However, in real-world populations at greatest risk—those with type 2 diabetes, obesity, and cardiometabolic risk factors—I would argue that we as providers are not identifying patients with cirrhosis because we are not applying these pathways early or widely enough.

G&H How does the development of cirrhosis complicate the disease burden of MASH?

WA Patients who have progressed to cirrhosis are at increased risk of developing hepatocellular carcinoma and liver failure; hence, this is the point at which surveillance and more intensive monitoring kick in.

Of course, disease burden can be measured in other ways as well. A lot of good data now show that quality of life drops off in patients with cirrhosis (often starting even before the development of cirrhosis), even though they may not have specific symptoms that relate to the liver. Both physical and psychological measures of quality of life fall, and probably related to that, there is also a societal

impact (eg, working days lost and decreased ability to care for others). Thus, there is a definite burden for patients with MASH who have developed cirrhosis.

G&H Being that there are no drugs approved for MASH cirrhosis so far, how are patients being managed at the present time?

WA Unfortunately, there are no drugs specifically licensed to treat or reverse the cirrhosis associated with MASH yet, although the development pipeline is looking optimistic. Thus, management is focused on optimizing behavior and lifestyle, improving cardiometabolic health, reducing risk factors for liver disease progression, and looking for and reacting to complications of cirrhosis. These include features of clinically significant portal hypertension such as varices and ascites and screening for hepatocellular carcinoma.

In March 2024, the US Food and Drug Administration approved resmetirom (Rezdiffra, Madrigal) for use alongside diet and exercise in patients with MASH and liver fibrosis consistent with stages F2 and F3, which does not include patients with cirrhosis. It is promising that there are a number of clinical trials underway for drugs to treat MASH cirrhosis. Most specialist centers have access to clinical trials (largely placebo-controlled) and can offer this option to patients who are interested and eligible based on the specific inclusion and exclusion criteria of each study.

G&H What are the biggest challenges of developing drugs for the treatment of cirrhosis in patients who have MASH?

WA One of the main challenges relates to safety. Even in patients with compensated cirrhosis, there are changes in function and blood flow that likely affect drug metabolism, although their extent and impact are variable between drugs and difficult to predict in an individual. The other main challenge is agreeing on what constitutes efficacy. Good evidence now exists that cirrhosis is architecturally reversible, but patients with cirrhosis could have very different patterns of scar tissue deposits that behave differently when it comes to resolution, introducing a degree of heterogeneity. Clinical endpoints will be key, and these will need appropriate numbers of participants and trial durations. Therefore, improvements in surrogate (ideally, noninvasive) markers are going to be very important for development in this space.

There is also the added issue of which patients are included in trials. Patients with many cardiometabolic risk factors are more likely to become cirrhotic; therefore, patients in MASH cirrhosis trials are likely to have a high burden of comorbidity and take a number of medicines. Some of these may have their own cardiometabolic-protective properties or may even have positive effects on the liver or on long-term outcomes, which would need to be accounted for in any trial. Similarly, polypharmacy increases the possibility of drug-drug interactions, which would also need to be studied carefully.

G&H What should be the goal of treatment for patients with MASH cirrhosis?

WA Patients may have a range of therapy goals. Most patients will want to know that their liver is getting better, so histologic improvement and reduction of clinical events are key to addressing that. In addition, it is important that the treatment addresses patient-reported outcomes such as key symptoms and quality-of-life endpoints. Whether a single medicine can meet all of these endpoints remains unknown, but as investigators, we should ensure that we continue to capture the data that matter to our patients.

> Combination therapy itself is not necessarily superior to a single therapy, but the right combination of medicines for the right patient—a move toward precision therapies—is an attractive proposition.

G&H What is the current landscape of the drugs in development for MASH cirrhosis?

WA This is an incredibly exciting time in the MASH space with lots of different medicines in development that target different pathways, from endocrine pathways, gut hormones, insulin sensitizers, and bile acid signaling to many more. Medicines already developed for obesity and/or metabolic conditions are also being assessed as treatments for patients with MASH cirrhosis. Taken together, these studies represent excellent opportunities to learn new biology. We will learn whether individual medicines work and, crucially, why or why not, therefore enabling us to refine the future development pipeline.

When there are many different classes of drugs, people's minds tend to move toward combination therapy,

especially when there are different goals of treatment. Combination therapy itself is not necessarily superior to a single therapy, but the right combination of medicines for the right patient—a move toward precision therapies—is an attractive proposition.

Indeed, the likelihood that disease in all patients with MASH cirrhosis is driven by the same mechanism is small. Clinicians will need to learn more about how to understand the different phenotypes, maybe even subphenotypes, of these patients in order to understand which processes are driving disease, and therefore how to select the best medicine. Newer and more innovative trial designs are going to be needed to address these issues.

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

WA The field has moved very quickly. Further work in epidemiology is needed to better understand how the disease is changing. As obesity rates have increased and the demographics of patients with type 2 diabetes have changed over the past 15 or 20 years, so too has the population with steatotic liver disease, including MASH cirrhosis. Providers are seeing younger patients in MASH clinics compared with 10 or 20 years ago, and that is true for other metabolic and liver diseases as well. In order to keep up with the shifting epidemiology, the field needs good data, which means that investment is needed in health care systems so patients with liver disease can be accurately identified, coded, and followed.

In addition, there is a need to prioritize continued research into the underlying mechanisms of disease in different patients. There remain great unmet needs in basic science, experimental medicine, and disease modeling in order to advance and refine knowledge, diagnosis, and treatments for MASH cirrhosis.

Disclosures

Professor Alazawi has received honoraria for speaking and consultancy from GlaxoSmithKline, Gilead Sciences, UCB Biopharma, Goldman Sachs, Thriva, Janssen, and Conclusio. He is a scientific advisor for Metadeq and is in receipt of competitive investigator-initiated funding from GlaxoSmithKline, MSD, and Gilead Sciences.

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.

Arnold J, Idalsoaga F, Díaz LA, et al. Emerging drug therapies for metabolic dysfunction-associated steatotic liver disease: a glimpse into the horizon. *Curr Hepatol Rep*. 2024;23:204-219.

Harrison SA, Loomba R, Dubourg J, Ratziu V, Noureddin M. Clinical trial landscape in NASH. *Clin Gastroenterol Hepatol*. 2023;21(8):2001-2014.

Lazarus JV, Mark HE, Allen AM, et al; on behalf of the Healthy Livers, Healthy Lives Collaborators. A global action agenda for turning the tide on fatty liver disease. *Hepatology*. 2024;79(2):502-523.

Zeng J, Fan J-G, Francque SM. Therapeutic management of metabolic dysfunction associated steatotic liver disease. *United European Gastroenterol J*. 2024;12(2):177-186.