MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

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Use of Resmetirom in Patients With Metabolic Dysfunction-Associated Steatohepatitis

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G&H Why was there a need to develop a therapeutic approach for metabolic dysfunction-associated steatohepatitis?

SH Between 30% and 40% of individuals in the United States have metabolic dysfunction-associated steatotic liver disease (MASLD), and of those, around a quarter will develop metabolic dysfunction-associated steatohepatitis (MASH). Thus, roughly speaking, there could be around 100 million Americans with MASLD and around 25 million Americans with the more aggressive form that could develop scar tissue. Once a patient develops stage 2 fibrosis, the risk of a liver-related complication increases 10-fold. Once a patient gets to stage 3, the risk increases 17-fold. Additionally, once at stage 3, approximately 20% of patients will progress to cirrhosis over a 2-year period.

Perhaps equally as important is the notion that once patients present with cirrhosis, there is not a lot that can be done. Many patients with unrecognized cirrhosis present when they have symptoms of liver disease and have a very poor prognosis. Recent data suggest that only a small percent of patients with MASLD or MASH have been diagnosed. Thus, there is a large unmet need to find patients. Prior to resmetirom (Rezdiffra, Madrigal), there was no US Food and Drug Administration (FDA)-approved treatment for this disease. One of the issues was that there was not a big push by providers to find these particular patients because there was no FDA-approved treatment.

Another important issue is the rise in incidence of MASH cirrhosis. According to Zhai and colleagues, in 1990 the global incidence was 178,430 cases. In 2017, that number had risen to 367,780 cases, an increase of nearly 106% over that 27-year period, and that was 7 years ago. Therefore, there is a large unmet medical need to find these patients, diagnose them, and get them the care that they need and deserve.

G&H What have been the challenges of drug development and approval in MASH?

SH It has been a challenge to get a drug approved in the United States because liver biopsies need to be done to diagnose the patient and to show that the liver has improved in the setting of treatment. It is important to note that in standard-of-care clinical practice, liver biopsies are not done anymore to diagnose MASH because they are invasive and associated with complications. Noninvasive tests can be used to make the diagnosis of moderate to advanced fibrosis in the setting of MASH with a high degree of certainty. It is hard to enroll trials where multiple liver biopsies have to be done. There are also very specific cells that have to be identified under the microscope by pathologists, including the elusive ballooned hepatocyte, which is challenging for pathologists to routinely find. Studies have been fraught with very high screen fail rates.

Additionally, along the way, we have learned from failures where we tried mechanisms that did not work. We realized the need to target upstream in the metabolic pathway, where the dysfunction begins. MASH is rooted firmly in an insulin-resistant pathway. Insulin resistance

makes adipocytes dysfunctional, causing them to release free fatty acids into the circulation. They are taken up in the portal vein into the liver, and there the hepatocytes have to quickly figure out what to do with these toxic fatty acids. Adipocytes can either burn these fatty acids through beta oxidation, or they can esterify them to triglycerides. That is what is seen under the microscope or on magnetic resonance imaging in the form of MASLD. Or, the fatty acids can be repackaged in the form of very low-density lipoprotein (LDL) and shipped out of the liver.

Unfortunately, in the setting of MASLD and insulin resistance, hepatocytes also become dysfunctional to the point where they do not efficiently beta-oxidize fatty acids, resulting in the accumulation of lipotoxic species. This is known as lipotoxicity and drives reactive oxygen species. It promotes inflammation and subsequent hepatocyte injury, ballooning, and apoptosis, subsequently leading to activation of stellate cells, which begin to lay down scar tissue. That is a normal wound-healing response to injury.

What we discovered is we need to hit targets high in that process, not down low, and ideally we need to be pleiotropic. We need to hit multiple targets with one medication, if we are able to, because that provides a better shot of shutting down the drivers of fibrosis and ultimately fibrosis itself. We need to understand that fibrosis portends a worse prognosis. Ideally, we want to target what causes the fibrosis and we want to target fibrosis directly as well because that allows us to get the maximum amount of wound healing that we can with one therapy. That is ultimately what got us to resmetirom.

G&H Could you expand on the mechanism of action of this drug and the rationale for studying it for the treatment of MASH?

SH Resmetirom is a thyroid hormone receptor–beta agonist. People often wonder why the thyroid is involved when talking about a liver disease. Interestingly, they are inextricably linked. In the setting of MASLD, the liver is relatively hypothyroid. Normally, when healthy, a person secretes T4 from the thyroid gland, which is an inactive prohormone. It is transported to the liver and, through the action of deiodinase 1, is converted to T3.

In the setting of MASLD, the patient's deiodinase 1 action is abrogated; it is not as active. Deiodinase 3 is upregulated and converts T4 to reverse T3. Thus, what we see in the setting of MASLD is lower deiodinase 1 activity and increased deiodinase 3 activity, leading to less conversion of T4 to free T3 and a buildup of reverse T3. This is seen playing out in the setting of MASH.

Because resmetirom is a thyroid hormone receptor–beta agonist, it is a thyromimetic. It is not a thyroid hormone, and it is highly selective to the liver. We know that in the setting of MASH, thyroid hormone receptor–beta is reduced. What we want to do is give a thyroid hormone receptor–beta agonist that is highly selective to the liver. When we do that, it allows several processes to occur that ultimately bring back online normal functioning of deiodinase 1, and we suppress deiodinase 3. The end result is more-normal conversion of T4 to T3, and we reduce the reverse T3 level.

Finally and uniquely, thyroid hormone receptor–beta agonists also reduce LDL cholesterol and have positive impacts on other lipoproteins involved with atherosclerotic coronary artery disease. That is an extrahepatic benefit of the drug.

G&H Could you discuss the key study data that led to FDA approval of resmetirom?

SH There were a number of key studies. The first was a phase 2A/2B trial published in *Lancet* in 2019. Patients with biopsy-confirmed MASH were enrolled and treated for 36 weeks. The primary endpoint was reduction in liver fat at 12 weeks, and the key secondary endpoints of MASH resolution without worsening of fibrosis and/or fibrosis improvement without worsening of MASH were included. Importantly, in that trial, the primary endpoint was hit. Resmetirom lowered liver fat content, but also hit on MASH resolution without worsening of fibrosis. Subsequently, when we used artificial intelligence digital pathology and fully quantified collagen content, we appreciated that the drug also had an impact on fibrosis improvement. As a result of that trial, Madrigal launched 2 major phase 3 trials, MAESTRO-NAFLD-1, which was published in *Nature Medicine* in 2023, and MAESTRO-NASH, which was the registrational trial for accelerated approval and was recently published in *The New England Journal of Medicine*. These 3 trials form the basis for the study data that led to the New Drug

> MASH resolution without worsening of fibrosis was achieved in 9.7% of the placebo group, 25.9% of the 80-mg dose group, and 29.9% of the 100-mg dose group.

Application filing and subsequent FDA approval of resmetirom for MASH.

MAESTRO-NAFLD-1 was a noninvasive trial, so no biopsies were done to get into the trial. It was predominately a safety study, so the primary endpoint was safety and tolerability. Secondary endpoints were key noninvasive tests to try to learn how the drug impacted certain important noninvasive parameters such as FibroScan, liver chemistry tests, and other blood-based biomarkers. More than 1200 patients were enrolled in that trial.

The major trial, MAESTRO-NASH, the registrational trial that allowed Madrigal to submit for accelerated approval, was a 54-month trial. An interim assessment was done at 52 weeks, when a second liver biopsy was done to see if patients improved their MASH and fibrosis. The first 966 patients who were enrolled and completed 52-week liver biopsies were considered in the published article and submitted to the FDA as part of the New Drug Application filing. In that trial, patients had to have a Nonalcoholic Fatty Liver Disease Activity Score of 4 or more with F1, F2, or F3 fibrosis. For the purposes of the FDA review, only F2 and F3 patients were included, but for the purposes of the filing, F1 patients were included.

At 52 weeks, liver biopsies showed that both doses, 80 mg and 100 mg, hit both endpoints. MASH resolution without worsening of fibrosis was achieved in 9.7% of the placebo group, 25.9% of the 80-mg dose group, and 29.9% of the 100-mg dose group. Fibrosis improvement without worsening of MASH was achieved in 14.2% of the placebo group, 24.2% of the 80-mg dose group, and 25.9% of the 100-mg dose group. Both doses were highly significant compared with placebo for both endpoints. A key secondary endpoint at 24 weeks looked at LDL cholesterol, which was 13.6% lower with the low resmetirom dose, 16.3% lower with the high dose, and 0.1% lower with placebo.

G&H In which MASH patients can resmetirom be used and how?

SH Importantly, the label specifically states which patients qualify for resmetirom treatment. It is a thyroid hormone receptor–beta agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic MASH with moderate to advanced liver fibrosis consistent with F2 to F3 fibrosis. It is important to understand that this is not a treatment for cirrhotics nor patients with no or mild fibrosis. We want to target patients who are at greatest risk of developing a liver-related complication short of stage 4 or cirrhosis, so those with F2 and F3 fibrosis.

The label states that resmetirom is to be used in conjunction with diet and exercise, which is important because we do not want to just give a pill for the disease; we want to foundationally try to change the root cause of the disease. When we are able to do that, hopefully one day we might be able to get away without having people on medical therapy. Diet and exercise driving weight loss are foundational to treat this disease. Resmetirom is added to therapy on top of that in patients with moderate to advanced fibrosis.

It is also important to note several other things from the label. This medication has not been studied in and is not intended to be used for patients who have had a liver transplant, nor is it intended for patients who are pregnant or on medications such as cyclosporine. The recommended dosing is based on body weight. Patients over 100 kg should use the 100-mg dose, and patients under 100 kg should use the 80-mg dose. Patients on clopidogrel need to start with a lower dose. Therefore, if patients happen to be on clopidogrel, which in the study 5% of the patients were, then they need to go to 60 mg if they are under 100 kg or 80 mg if they are above 100 kg. It does not matter if patients take this medication with or without food.

> … it is important to note that resmetirom is incredibly safe and well tolerated.

There is also guidance around statin dosing that is important to briefly mention. Providers need to read the label and understand that if a patient is on a concomitant statin, there is a maximum dose of statin that should be used. For instance, atorvastatin is recommended to not exceed 40 mg daily. It is also important to remember that resmetirom has a significant impact on lipoproteins in lowering LDL cholesterol, triglycerides, lipoprotein-a, apolipoprotein C-III, and apolipoprotein B-100.

G&H Are there challenges in accurately identifying patients with the stages of fibrosis that are eligible for resmetirom treatment?

SH Since we do not have to use liver biopsies to make the diagnosis of MASH with moderate to advanced fibrosis, what can we use? The noninvasive tests that will be utilized and the cut points for these tests are evolving. The American Association for the Study of Liver Diseases (AASLD) recently released updated guidance. I would point to the study data because that is where we get the best information around these types of patients

using noninvasive tests. When looking at the baseline characteristics of patients with stage 2 to stage 3 fibrosis in the registrational trial, there were 2 main noninvasive parameters that were used. One was FibroScan or vibration-controlled transient elastography. The other was the Enhanced Liver Fibrosis (ELF) test, for which AASLD guidelines define at risk as greater than 7.7. One of the things we have been talking about is selecting appropriate patients. The agent is likely safe in cirrhosis without clinically significant portal hypertension, although we await these data.

G&H Do you have any other guidance regarding how to find initial patients?

SH What we need to do is begin to find patients who are at greatest risk of moderate to advanced fibrosis and disease progression because this is a silent disease. Most patients do not know they have this disease. It starts with identifying risk factors. If a patient has any family history of MASLD, they are at risk. Diabetes is the greatest risk factor for this disease, followed very quickly, if not equally, by obesity. Having metabolic syndrome (meaning a patient has hypertension, hyperlipidemia, and is overweight) is another risk factor. An easy group to start with would be patients with diabetes, as the risk of MASLD is very high and these patients are often in multidisciplinary care. We know that 70% of them have MASLD. A third of them have MASH, and around 17% of them have advanced liver disease at the time of diagnosis. Those are people we would absolutely want to be managing. It is a little like worrying about the eyes, kidneys, and nerves of diabetic patients; we should also be worrying about the liver in this population. Screening can be easily done if providers have access to transient elastography or the ELF test. AASLD guidelines recommend additional testing in patients with liver stiffness measurement greater than 8 kPa or an ELF score of 7.7.

G&H What adverse events have been reported so far, and are there any potential safety concerns?

SH First of all, it is important to note that resmetirom is incredibly safe and well tolerated. The common adverse reactions reported with the drug are mainly gastrointestinal-related and generally transient with resolution over time. The way the FDA reported this in the package insert was with exposure-adjusted incidence rates, which are an estimated number of first occurrences of the adverse reaction of interest if 100 patients are treated for 1 year. To give an example, the most common adverse event with resmetirom was diarrhea. It lasted, on average, 2 to 3 weeks and was often characterized as loose stool or worsening of underlying diarrhea. It would have occurred in 33 patients out of 100 if those patients were all treated for 1 year. At the low dose of resmetirom, the rate would have been 23 out of 100 patients, and with placebo, 14 out of 100. For nausea, those numbers would have been 15 with the high dose, 18 with the low dose, and 9 with placebo.

G&H How should patients be followed after starting this treatment?

SH We know that resmetirom works over time. Ideally, the way I would follow patients is I would start them on therapy after an appropriate noninvasive test to diagnose MASH with moderate to advanced fibrosis, and I would check liver chemistry tests at 12 weeks, 24 weeks, and 1 year and, if there is access to transient elastography, I would use it at 24 weeks and 1 year. What we know about resmetirom and liver chemistry tests is that they should gradually fall over time. There might be an initial slight bump, up to a max of 1.5 times baseline at 4 weeks, so

> The important take-home point is that providers need to do a good job of ruling out coexistent underlying liver disease, specifically cholestatic liver disease …

I do not recommend obtaining liver chemistry tests at 4 weeks. This is no different from statins, where there could be a slight bump when therapy is initiated. There were no adverse reactions relative to hepatotoxicity in MASH patients treated in the trial, so that gives me encouragement to check liver chemistry tests just at 12, 24, and 52 weeks. Providers might also want to check a lipid panel at 24 weeks because this drug does have a positive impact on lipids as well.

Although safety data from 2000 MASH patients were submitted and there were no hepatotoxicity cases in any patients who had MASH, there was 1 hepatotoxicity case, which I think should be mentioned. It turned out that this patient did not have MASH and actually had underlying autoimmune liver disease, most likely primary biliary cholangitis (PBC). Essentially, this patient had liver chemistry test flares while on resmetirom and

initially after approximately 2 months of treatment. The liver chemistry test returned to normal shortly after stopping the drug. While off the drug, the liver chemistry test flared again and then gradually improved. Finally, at approximately two-thirds of the year into the study, the patient was restarted on medication, and the liver chemistry test flared a third time but also in the setting of acute cholecystitis. This was a very complicated case.

The important take-home point is that providers need to do a good job of ruling out coexistent underlying liver disease, specifically cholestatic liver disease such as PBC as well as autoimmune hepatitis. This could be done by using autoimmune biomarkers. We know in this particular case, antinuclear antibodies and antimitochondrial antibodies were quite elevated. Just like we rule out viral hepatitis and iron overload, we need to make sure we are doing a good job of looking for autoimmune liver disease. Ideally, we would not want to initiate resmetirom therapy in the setting of untreated autoimmune liver disease.

G&H What are the next steps in research?

SH MAESTRO-NASH is still ongoing, out to 54 months. The intent is to do a third liver biopsy at 54 months with the outcome of interest being progression to cirrhosis. More than 1700 patients are enrolled in the entire trial who are marching toward that 54-month time point. Although the drug is conditionally approved, with what we call accelerated approval, we have to show that the surrogate of fibrosis improvement and MASH resolution translates into a hard outcome. The hard outcome of interest here is preventing progression to cirrhosis. Another phase 3 trial that has recently launched is MAESTRO-OUTCOMES. Patients who have well-compensated cirrhosis are being enrolled and randomized to treatment with resmetirom vs placebo, and will be followed to a hard outcome (liver decompensation, liver transplantation, or death). Longer-term data are also needed to assess long-term efficacy of the drug. We also need to look at subpopulations. We did study a good number of Hispanic and White patients, but there are ethnic groups that we need to focus on a little more. We have not studied many Asian or African American patients. Additionally, combination therapy is going to be the wave of the future. There are a number of good drugs that could theoretically be combined with resmetirom, but those need to be studied in future trials.

Disclosures

Dr Harrison's disclosures were not available at the time of publication.

Suggested Reading

Harrison SA, Bashir MR, Guy CD, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet.* 2019;394(10213):2012-2024.

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Sadly, Dr Harrison passed away in April 2024. He was a leader in the field of hepatology, particularly MASH, and was pivotal in the development of resmetirom. He served as the section editor of G&H's *MASH in Focus column since its inception in March 2020. He was passionate about highlighting clinically relevant topics in the column and always made time for his editorial duties. All of us at* G&H *send our condolences to his family and friends. We greatly appreciate all of his contributions to the journal and will miss his enthusiasm and expertise.*

This column is based on an interview with Dr Harrison at the beginning of April 2024. It was reviewed in his place by Dr Nancy S. Reau, G&H's *section editor of hepatology.*