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Advances in MASLD/MASH: Treating the Liver, the Disease, and the Patient – Chair's Perspective

Announcer:
Welcome to CME on ReachMD. This activity, titled "Advances in MASLD/MASH: Treating the Liver, the Disease, and the Patient – Chair's Perspective" is provided by Prova Education.

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Dr. Alkhouri:
Hi, this is CME on ReachMD, and I'm Dr. Naim Alkhouri, the chief medical officer at Arizona Liver Health in Phoenix, Arizona. Today I will be highlighting the key messages presented at a satellite symposium by Prova Education at a recent meeting in San Diego, California.

So we estimate that at least 2 million adults in the United States may have high-risk MASH, and this is based on data from the NHANES database. And in fact, other studies estimated that up to 15 to 16 million Americans may have significant fibrosis due to MASLD and MASH. The combined burden of MASLD and MASH in North America is expected to increase by up to 82% in the next 15 years.

So I'm going to walk you through this case of a 56-year-old Hispanic woman that was referred by her PCP because of elevated liver enzymes. She is currently on a statin, atorvastatin 80 mg daily for dyslipidemia, and she takes losartan for hypertension. Her BMI is at 42 kg/m^2, indicating class 3 obesity. And you can see her blood pressure is not well controlled at 139/84. Lipid panel showed LDL cholesterol at 98, hemoglobin A1c at 6.2, indicating prediabetes. The ALT was elevated at 90 units per liter, AST at 76, and she had no more albumin and platelet count of 202,000

So this patient came to a specialty clinic, and she had vibration-controlled transient elastography to measure liver stiffness. And the liver stiffness came back at 10.9 kPa, consistent with significant fibrosis. And the CAP score for steatosis came back at 343, indicating significant steatosis.

So we have a risk stratification algorithm that was adopted by the American Association for the Study of Liver Disease, AASLD. We start in the primary care and endocrinology clinics with a primary risk assessment with the FIB-4 index that includes the patient's age, AST, ALT, and platelet count. If the FIB-4 is less than 1.3, this indicates lower risk for advanced disease, and these patients can be followed in primary care with the focus on a lifestyle intervention. And if the FIB-4 is more than 2.67, these patients need to be referred to a specialist. And then if the FIB-4 is between 1.3 and 2.67, we need to do a secondary risk assessment, either with transient elastography or with the enhanced liver fibrosis test, which is a serologic blood test that can help determine the severity of fibrosis. It is very important to do a cardiometabolic risk reduction intervention in all these patients.

And then once the patients are referred to a specialty clinic, we utilize more advanced technologies such as MR elastography, corrected T1, and some combination scores to determine the presence of at-risk MASH, defined as MASH with significant fibrosis.

So what additional tests would I consider to assess my patient with at-risk MASH?

Well, now I have a patient who is from a Hispanic ethnicity, so higher rates of MASLD and MASH. She has prediabetes, dyslipidemia, hypertension, so she has the metabolic syndrome. So this patient has high pretest probability of having at-risk MASH. The transient elastography measurements that we did showed steatotic liver disease, but also evidence of significant fibrosis.

But if I want to increase my confidence level and positive predictive value, I may consider calculating a score called the FAST score. The FAST score stands for FibroScan plus AST, and it has 3 variables in it. The first one is liver stiffness measurement in kilopascals. The second one is the controlled attenuation parameter, or CAP score, that estimates the amount of steatosis. And then the last parameter is the AST liver enzyme that will help us learn about disease activity. So we put these three variables in one online calculator, and you get a FAST score that ranges from 0 to 1. And the FAST score that is less than 0.35 indicates low likelihood of having at-risk MASH, which is defined as MASH plus F2 fibrosis or higher. And then if you have a FAST score more than 0.67, this indicates high likelihood of having at-risk MASH. So this is what we call the rule-in zone for at-risk MASH. FAST score was developed in an original cohort in the United Kingdom and has been validated in several international cohorts.

So going back to our case, we calculated the FAST score. And in this patient, the FAST score was at 0.74, so this is more than 0.67. So this increases my positive predictive value and confidence that this patient will have at-risk MASH.

So in patients with at-risk MASH, these are what we call the target population for pharmacologic treatments that are in development, but also for FDA-approved treatment, which the only one we have today is resmetirom, which is a thyroid hormone receptor beta agonist. So the indication for resmetirom is for patients with at-risk MASH, which is defined as the presence of MASH plus F2 and F3 fibrosis. It's not indicated for early disease, so MASH with F0/F1, you are not supposed to use resmetirom today. It's also not indicated for patients with cirrhosis, which is F4 fibrosis.

So how would I initiate treatment in this patient? Again, first you need to determine disease severity, and then you can prescribe resmetirom based on the data from the MAESTRO-NASH phase 3 trial. This was a study that randomized patients with MASH and non-cirrhotic fibrosis, including 966 patients with biopsy-proven disease. They were all treated for 52 weeks and had a repeat liver biopsy to look at two primary endpoints. The first one was MASH resolution on the repeat biopsy, and this was achieved in up to 30% of patients on resmetirom. And this was significantly better than the placebo arm. And the second endpoint was fibrosis regression by one stage, and this was achieved in about 25% of patients on resmetirom. Resmetirom was well tolerated in the phase 3 MAESTRO-NASH trial with very low discontinuation rate. And the two most common adverse events were mild nausea and mild diarrhea that can be managed easily in the vast majority of patients.

Again, I want to highlight that the target population for resmetirom is patients with F2 and F3 fibrosis. So resmetirom is a liver-directed therapy. It has proven effects on liver fibrosis. And these are the patients that we want to treat. Of course, it can be also combined with the GLP-1 receptor agonist. And in fact, in the MAESTRO-NASH trial, 15% of patients were on a baseline GLP-1 therapy, and then they were started on resmetirom.

Would I order a liver biopsy to evaluate my patient? The short answer is no in the vast majority of patients, because we are able to risk stratify them based on noninvasive tests. However, when you have discordance between two noninvasive tests, let's say the transient elastography is showing high liver stiffness but then the enhanced liver fibrosis score is showing low score for fibrosis, then you may need to do a liver biopsy to really determine the stage of fibrosis.

Now in this figure here, you see the algorithm for deciding how to start resmetirom treatment. This was from a consensus paper that I co-authored with a few of my colleagues, and we divided the patients into 3 zones.

So we have what we call the green zone. This is the sweet spot when you can treat patients with resmetirom with confidence based on noninvasive tests. And what we utilize here is transient elastography between 10 to 15 kPa. You can also use MR elastography between 3 to 4.2 kPa, or the ELF score between 9.2 to 10.4. And of course, if you have a historic biopsy showing MASH with F2/F3 you can utilize resmetirom in all these patients.

And then we move on to the yellow zone, where you can actually use resmetirom, but with caution to make sure that the patient does not have cirrhosis. And this indicates transient elastography between 15 to 20 kPa, MR elastography between 4.2 to 5 kPa, ELF score between 10.5 to 11.3.

And then we have the red zone where you should not use resmetirom. And these are patients with liver stiffness more than 20 kPa, MRE more than 5 kPa, or ELF score more than 11.3.

Once you start to resmetirom, you need to monitor for both safety and efficacy. And what I do in my patients for safety, I measure liver enzymes at baseline, and then at 3, 6, 9, and 12 months. And then in terms of efficacy assessment, I measure baseline noninvasive tests [NITs], including my liver stiffness. I quantify liver fat on the CAP score, MRI-PDFF, and I measure the ALT. And then at the 6-

month mark, I repeat my NITs, and then I repeat them again at 12 months. And this is important to understand that you should not determine futility or response to resmetirom until you treated the patient for about 12 months.

And then you look at the totality of the data. If you see a reduction in ALT by 17 units from baseline, or 20% from baseline, you see a reduction in liver stiffness by 25% from baseline, and you see a reduction in liver fat on MRI by 30% relative reduction, this is a great response, and you need to continue resmetirom in this patient, because they are actually getting the benefits from this medicine. If you do not see any improvement in the noninvasive tests, obviously the medicine is not working, and this is the definition of futility, and you can stop. And then if you see improvement in some of the NITs but not all of them, typically in my clinic I would continue the treatment for an additional 6 to 12 months, I repeat my NITs, and then I decide if I want to continue treatment.

Would I prescribe a GLP-1 receptor agonist to my patient? I may actually consider adding the GLP-1 after I start resmetirom and after I have them on a stable dose of resmetirom for 6 months or so. And semaglutide might be a good indication for someone with class 3 obesity and prediabetes. It's actually recommended in the AASLD and EASL guidelines for the non-MASH indications. So the type 2 diabetes indication and the obesity indication. And we know the GLP-1 receptor agonists have proven cardiovascular benefit in patients with type 2 diabetes, but also in patients with obesity without type 2 diabetes, based on the SELECT trial.

So I see a future where we actually combine resmetirom with the GLP-1 agonist. Resmetirom, as I mentioned earlier, is liver directed. It works on liver fibrosis. It's indicated specifically for patients with MASH and F2 and F3 fibrosis. But then it's weight neutral, and it's not going to help with insulin sensitivity, so adding the GLP-1 may help patients lose weight. It will help with insulin sensitivity, and potentially it may have some synergistic effects with resmetirom. I can see some patients starting on a GLP-1, especially with early fibrosis, and that might be adequate for some patients. But we know that there are many patients that will go on a GLP-1 and continue to have F2 and F3 fibrosis. We know that some patients do not tolerate GLP-1 agonists because of the adverse events. There is a category of what we call lean MASH. These are patients with normal BMI, and they have MASH and significant fibrosis. And resmetirom might be a better option for these patients. So I think again, these two medications may work together and the combination might be indicated in some patients.

So with this, I'm going to conclude this case. Thank you so much for joining me. Unfortunately, our time is up. This has been CME on ReachMD.

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