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Treating MASH With Compensated Cirrhosis: A Serious Unmet Need

Announcer:
Welcome to CME on ReachMD. This activity, titled “Treating MASH With Compensated Cirrhosis: A Serious Unmet Need” is provided by Prova Education. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Alkhouri:
Hello, everyone. I'm Dr. Naim Alkhouri, the Chief Medical Officer at Summit Clinical Research and the Chief Research Officer at the Clinical Research Institute of Ohio. And today I will be discussing how to treat MASH with compensated cirrhosis, which is a serious unmet need.

First, I want to start with this case presentation. We have a 57-year-old male with type 2 diabetes and MASH who was referred to your clinic for a new consult. BMI at 29.4 so overweight. AST is at 77, ALT at 67 so mildly elevated with the AST being higher than ALT. And then the platelet count is at 152,000 so borderline low. The patient is asymptomatic with no liver-related symptoms. However, the liver ultrasound shows an echogenic liver, and there is splenomegaly with the spleen measuring 15 cm in the largest diameter.

What are your next steps? Does this patient have cirrhosis? If the patient has cirrhosis, what stage are we talking about? Do we have clinically significant portal hypertension or not? Would you do an upper endoscopy to screen for varices? And then what are the management goals to prevent decompensation?

So the first question is, does this patient have MASH cirrhosis? And to do this, we have several things we can look at. Number one, we can calculate the FIB-4 index. This is a simple score that only requires your AST to ALT ratio, your age, and platelet count. And we've discussed in MASH patients that having a cut-point above 2.67 typically indicates the presence of advanced fibrosis. But actually there is another cut-point which is more than 3.48 which typically indicates the presence of cirrhosis. So I want you to remember this cut-point for cirrhosis, 3.48. And if you calculate the FIB-4 in this patient, it comes at 3.53, so this should raise your suspicion that this patient may have actually cirrhosis.

Next, we do our vibration-controlled transient elastography, VCTE, to measure liver stiffness, LSM, and this can be done with different machines. And in this case, the liver stiffness by VCTE comes back at 26 kilopascal. With VCTE, we know that the cut-point for cirrhosis starts around 14, and typically, anything more than 25 indicates the presence of clinically significant portal hypertension. So in this case, again, VCTE of 26 kilopascal indicates high likelihood of having cirrhosis.

However, we've known from different studies that the positive predictive value of VCTE sometimes is not optimal, and that's why we have scores that can help optimize the positive predictive value for VCTE, including the Agile 4 score that was developed to predict the presence of cirrhosis, and again, increase your positive predictive value.

So to calculate the Agile 4, you have your VCTE, liver stiffness in kilopascal. You also have your AST/ALT ratio, your platelet count, gender, age, and if the patient has type 2 diabetes or not. You put all these numbers and clinical characteristics in a mathematical equation, and then you will get an Agile 4. This was developed initially in an internal cohort that included 700 patients, and was subsequently validated in two large external cohorts.

And when you get the Agile 4 score, you're going to get a score that ranges from 0 to 1. Having an Agile 4 less than 0.25 indicates the absence of cirrhosis, so this is the rule-out cut-point. And having an Agile 4 above 0.57 indicates the presence of cirrhosis, so this is the rule-in cut-point that maximizes the positive predictive value. So again, if you obtain your liver stiffness, and you want to increase your positive predictive value, you may calculate the Agile 4.

So in our case, we have a liver stiffness of 26 kilopascal consistent with cirrhosis. We have a FIB-4 of 3.5, above the threshold for cirrhosis. And if you calculate the Agile 4, it comes at 0.74, so this is above the 0.57 cut-point.

Now I have several lines of evidence, all of them are showing me that this patient has cirrhosis. So in my clinic, I would confirm the diagnosis of cirrhosis. There is no need to do a liver biopsy. And this is a patient that I would start HCC surveillance—hepatocellular carcinoma surveillance—with liver imaging plus alpha-fetoprotein every 6 months.

Next, I want to see does the patient have clinically significant portal hypertension? And these are the Baveno criteria, and what we call the Rule of Five. So having liver stiffness less than 10 kilopascal can exclude what we call CACLD, which is compensated advanced chronic liver disease. This is typically having stage 3 and 4 fibrosis, so F3/F4 fibrosis.

Having a liver stiffness above 25, that indicates the presence of cirrhosis with clinically significant portal hypertension. And then in patients with liver stiffness between 15 to 25, depending on the platelet count—when the platelet count is low, that also indicates the presence of clinically significant portal hypertension.

You may also look at other lines of evidence, including FIB-4, enhanced liver fibrosis test, ELF, and then, of course, we have MR elastography as well.

But again, I wanted to share this because I think it's very important when we diagnose someone with cirrhosis to see if they have clinically significant portal hypertension. If you recall, our patient had a kPa number of 26 so that indicates the presence of clinically significant portal hypertension. And if the liver stiffness in our patient was at, let's say, 22 and the platelet count was less than 150,000, that will also indicate the presence of clinically significant portal hypertension.

When we look at cirrhotic patients, we divide them into compensated and decompensated. So decompensated, we all know this means the development of complications like ascites, hepatic encephalopathy. But even within the compensated group, we look at patients with compensated cirrhosis without clinically significant portal hypertension. And then we have those with clinically significant portal hypertension based on the Baveno criteria. And then we have patients also with varices, and we divide these into small and then large, what we call varices needing treatment, or VNTs.

So this is how we think about patients with compensated cirrhosis, and making the diagnosis of clinically significant portal hypertension is very important for management.

So question number 2 in this case, what are the next steps to prevent hepatic decompensation?

So now we know the patient has cirrhosis, and our goal is to prevent decompensation and hopefully avoid a liver transplant. So the management should aim at preventing progression and not just treating complications as they come.

And today, we don't have any treatment that can reverse cirrhosis and take a patient from stage 4 to stage 3. But I say yet, because we have very promising agents in development.

We have two approaches that can be taken to prevent progression. Number one is to suppress the upstream injury, and we've seen this when we cure hep C, when patients that drink alcohol and they stop drinking, that can help you know maintain the liver. And in patients with MASH, weight loss is still important, even when they progress to compensated cirrhosis. And then we can also target key factors in

the pathogenesis of decompensation and progression.

And I think the main thing we can do is really to initiate beta blockers—non-selective beta blockers—or carvedilol in patients with clinically significant portal hypertension. The beta blockers we use in patients with cirrhosis, we prefer carvedilol now because of its ease of use, less adverse events, and evidence that it may decrease portal pressure more than other beta blockers. So this is the preferred agent. And typically you want to up-titrate through the 12.5-mg dose. And you know you monitor the blood pressure, of course, and sometimes you are limited with how high you can go.

Alternatives to carvedilol include nadolol and propranolol. And patients that do not tolerate beta blockers, of course, you know endoscopic banding as needed in patients with large varices.

But one message I want to convey to you today is that you know these beta blockers go beyond just preventing variceal bleeding to preventing decompensation. And this evidence was generated in the PREDESCI study, where about 200 patients were randomized to receiving beta blockers with propranolol or carvedilol versus placebo. And all these patients had documented clinically significant portal hypertension based on hepatic vein pressure gradient.

And what we learned from the PREDESCI study is that patients in the beta blocker group in the red line here had lower incidence of decompensating events. You see the hazard ratio of 0.51, so almost 50% reduction in developing the primary endpoint, which is basically decompensation or dying.

When we looked at the decompensating events—I think this is very important to highlight here—you see that there was significant reduction in the beta blocker group and the development of ascites. So actually being on propranolol or carvedilol in patients with clinically significant portal hypertension decreased the development of ascites. And that's why I said that these beta blockers are able to prevent decompensation period, not just from variceal bleeding. Actually, in this study, there was no difference on the incidence of gastrointestinal bleeding, but of course, the number of events was low, and we may need a larger study to show a benefit on preventing GI bleeding.

So I think we have a new paradigm in the management of compensated cirrhosis. We used to say that in every patient with cirrhosis, you need to do upper endoscopy to look for varices. And then, based on the presence or absence of varices, you develop the management plan with beta blockers or band ligation.

But the new paradigm says that if you diagnose someone with cirrhosis, look at the Baveno criteria, obtain liver stiffness measurement and platelet count. And if the patient has evidence of clinically significant portal hypertension, you actually need to start carvedilol to prevent decompensation. And if they don't have evidence of significant portal hypertension, then you continue to monitor with liver stiffness and platelets on a yearly basis.

So if you follow this algorithm, you don't need to do a routine endoscopy on every patient, and you can initiate the carvedilol early on to prevent decompensation.

Nutrition is very important also in the management of patients with compensated cirrhosis from MASH. We have to keep in mind that the majority of these patients still have obesity, so we need to decrease their caloric intake, and this depends on their baseline BMI.

It is very important in patients with cirrhosis to increase protein intake, and my target typically in my clinic is to do 1.5 grams of protein per kilogram of body weight. And in decompensated patients, typically we try to aim higher if they can tolerate it. Patients with cirrhosis are at risk for sarcopenia, so it's very important that they consume enough protein. And it is important also to avoid fasting in patients with cirrhosis, because they tend to utilize the protein in their muscles and amino acids to produce energy, and that's the last thing we want in patients with cirrhosis.

So going back to our case, we diagnosed this patient with compensated cirrhosis. That, by itself, requires initiating HCC surveillance with imaging and alpha-fetoprotein every 6 months. Next, we diagnosed the patient with clinically significant portal hypertension based on a liver stiffness of 26 kilopascal—above 25—so we initiated carvedilol at 6.25 mg daily initially with up-titration and monitoring. And again, this is regardless of doing an upper endoscopy and looking for varices, and again, this is to prevent decompensation. And then we would give this patient a nutrition prescription based on the weight and the BMI to decrease the caloric intake and target about 120

grams of protein daily.

I want to share with you some promising data with new agents that might be able to reverse cirrhosis. The first study I'm sharing with you here is called the SYMMETRY trial. This was looking at patients with biopsy-proven MASH cirrhosis, so stage 4 on the biopsy, that were treated with a fibroblast growth factor 21—FGF21—called efruxifermin, for 2 years, or 96 weeks.

And on the repeat biopsy with the high dose of efruxifermin 50 mg weekly, almost 40% of patients were able to reverse cirrhosis and go from stage 4 to stage 3, and this was significantly better than placebo in the completers analysis. And then we also saw in the intent-to-treat analysis, which is a more strict way to analyze the data, that up to 29% of patients were able to reverse cirrhosis with efruxifermin 50 mg compared to 11% in the placebo arm, again significant difference.

The second agent that showed promising results in patients with cirrhosis is resmetirom, which is a thyroid hormone receptor beta agonist that was approved by the FDA in 2024 to treat patients with F2/F3 fibrosis. But in an open-label study that treated 122 patients with resmetirom for 2 years, there was significant reduction in liver stiffness on VCTE by up to 6.7 kilopascal. A reduction in a cirrhotic patient by more than 5 kilopascal is clinically significant. There was also more than 50% of patients that achieved reduction in liver stiffness from baseline by 25% or more. And then in about 35% of patients after 2 years of treatment, we saw potentially reversal of cirrhosis, defined as liver stiffness less than 15 kilopascal after 2 years of treatment, and also a reduction in liver stiffness by more than 25%.

So very promising results. And we are studying these agents now in phase 3 trials for patients with compensated cirrhosis. And we expect some results, hopefully in 2027.

So my take-home message is that we need to classify our patients correctly within the spectrum of cirrhosis. Not all compensated cirrhosis is created equal, and we need to know if they have clinically significant portal hypertension. The goal is to prevent decompensation, and this can be achieved with weight loss, non-selective beta blockers or carvedilol, and also exercise very important in this population. And finally, reversing cirrhosis with new therapeutic agents is potentially becoming a reality, and we are hopeful that we will see positive results from phase 3 programs.

Thank you so much for joining me for this educational video, and I hope to see you again in the near future.

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