What's Hot and What's Next: Mastering MASH-Specific Therapies That Deliver

CMEO Podcast Transcript

Sonal Kumar, MD, MPH:

Hello, I'm Dr. Sonal Kumar, thank you so much for joining us for *The Glow-Up Era of MASH Management*. This initiative is supported by an educational grant from Novo Nordisk Incorporated. This is the third of four CMEO Snacks in the series. Today's episode will address U.S. Food and Drug Administration (FDA)-approved metabolic dysfunction-associated steatohepatitis (MASH)-specific therapies, which we now have two of. Again, my name is Sonal Kumar. I'm an assistant professor of medicine at Weill Cornell Medical College in New York, New York. I have both clinical and research interest in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and specifically within multidisciplinary care, and I'm very pleased to be joined today by Dr. Zobair Younossi, who of course needs no introduction but I will ask him to introduce himself nonetheless. Dr. Younossi?

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Hi Sonal. It's wonderful to be with you and to be a part of this wonderful program. I'm Zobair Younossi. I'm the Professor and Chairman of the Global NASH/MASH Council. I've been in the field for liver disease research and specifically in the area of NASH/MASH for about 30 years, doing different types of research including outcomes, research epidemiology, clinical trials, and non-invasive testing (NIT) sort of assessment, etc. So I'm delighted to be here.

Sonal Kumar, MD, MPH:

Great. I'm looking forward to our discussion. So, here's our learning objective for today's program: After participating in this activity, learners should be able to better identify available MASH-specific therapies appropriate for timely management in concordance with treatment guidelines and care pathways. Let's get started. Today is the third of a four-part snack series following the case of our patient Mr. B. We'll start with a little recap of Mr. B. He's 61 years old. He's a utilities field crew chief. He was seen just for a routine follow-up visit and didn't really have any complaints. No abdominal pain, fatigue, arthritis, or history of jaundice. His pertinent medical history includes type 2 diabetes, dyslipidemia, and hypertension. He is also overweight with a body mass index (BMI) of 29.1. As far as alcohol consumption goes, he has an occasional glass of wine with dinner, and the medications that he's on right now are metformin, valsartan, and hydrochlorothiazide.

His physical exam was unremarkable. When looking at his lab values, his liver tests were all essentially normal. Just a couple of things to point out. Bilirubin was 1, his platelets were 110,000, and his cholesterol low-density lipoprotein (LDL) was 130, triglycerides 235, and A1C was 7.1%. The first step in his assessment was to do primary risk assessment. He had a Fibrosis-4 (FIB-4) score of 2.59, which puts him in the indeterminate category. He also had an abdominal ultrasound just to make sure nothing else was going on. It showed hepatic steatosis. No real hepatic lesions, no ductal dilatation, no ascites, because his FIB-4 score was indeterminate. Then he had subsequent secondary testing. First, he had a FibroScan that was 9 kilopascals, but the interquartile range (IQR) was a little bit on the higher side, so he had further testing with magnetic resonance elastography (MRE), which showed a score of 4.2 kilopascals. He also had an enhanced liver fibrosis (ELF) score of 10.2, essentially confirming MASH with fibrosis.

Before we get into the discussion, let's get the audience involved. Which of the following would you consider for treating Mr. B? A: lifestyle intervention, just using nutrition and exercise; B: resmetirom; C: semaglutide; D: resmetirom and semaglutide; or E: I'm not sure. There isn't necessarily one correct answer to this question. Let's talk about our options. Dr. Younossi, would you agree that this is a patient with type 2 diabetes who is eligible for MASLD and MASH therapy? And if you agree that this patient should be treated, which therapy would you choose and why?

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Yes, thanks Sonal. There are a few things that when you look at this patient even before doing NITs that should raise some issues. First of all, you've got a patient with three components of metabolic syndrome, that's dyslipidemia, diabetes, and hypertension, he's male, and then you look at the labs. Despite the fact that the liver enzymes are normal, his platelet count is low. This suggests, to me, advanced liver disease. So, even without doing a FIB-4, you'd know that you're dealing with a patient who has high suspicion of having advanced liver disease or at least advanced fibrosis, not advanced liver disease. So, now of course that was confirmed with FIB-4 followed by a transient elastography, but I think when you have a patient like this, do a secondary NIT. I wouldn't stop with just one secondary NIT because you want to make absolutely sure that the patient doesn't have cirrhosis, because currently the drugs that are approved should not be used in patients with cirrhosis. So, doing that second NIT, here they have done three secondary NITs, which are vibration-controlled transient elastography (VCTE) and then MRE and then an alanine transaminase (ALT) test. All of those suggest that the patient has probably F3. If the ALT test was more than 11.3 or if we had a VCTE of 20 kilopascal or higher, then I would say that patient probably has cirrhosis and I wouldn't treat, but here I think you could treat pretty reasonably consistent with the current guidance. Now, the question is what are you treating? The first thing to do is that, regardless of what drug you're going to use that will target MASH, you have to use lifestyle issues and address that the patient probably should consider some form of exercise. And as you know, these patients also have some sarcopenia from time to time that you want to address.

So, both sort of physical activity, both in terms of muscle resistance as well as other types of cardiovascular improvement will be important, and looking at diet to make sure that ultra-processed food is really not included in the diet, and excluding those would be one way to do this, but then you have a treatment of diabetes that's probably not optimal in a patient like this. If the patient is on metformin, and we could get into this a little bit more, that's probably not the ideal treatment of diabetes in this patient. I would probably treat the comorbidities of diabetes and obesity, I mean he's overweight, at least probably with a glucagon-like peptide-1 (GLP-1) agonist. The question is, if he's on that treatment, should you also start the other drug that's approved and that's been approved for over a year, which to me is resmetirom? He certainly is a candidate for resmetirom also.

What if you start them both at the same time? It's sort of a flip of a coin, if the patient can actually tolerate it, and the insurance, the payers, cover both. I don't have a problem with starting these shortly one after each other. I wouldn't start both drugs all at the same time because I don't have the evidence about tolerability. I'm not too concerned about side effects of hepatotoxicity, but I am concerned about tolerability, especially with the GLP-1 receptor agonists, sort of gastrointestinal (GI) side effects. So, if I have to start something, I may start resmetirom or I may start semaglutide, but very shortly after that I probably will consider both for this type of patient because the American Diabetes Association (ADA) guidance that was published earlier, or guideline that

was published earlier this year, and also the global guideline or recommendation we published in *Gastroenterology* this past month would recommend that you treat the comorbidities and then also have targeted treatment for MASH in a patient that has F2 or F3, and the patient has F3.

Sonal Kumar, MD, MPH:

Yes, I completely agree. I think in patients that I suspect have a little more advance disease, more towards the F3 side, which, like you said, for this patient, his platelets are low and he has multiple comorbidities. Especially with diabetes, I tend to be a little aggressive with them and I will start, like you said, stagger them, but be quick to start both medications and then which one you start first is sort of a toss-up. I completely agree.

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Absolutely.

Sonal Kumar, MD, MPH:

Here are the FDA indications for the two approved MASH therapies in the United States, so what we have available. First there's resmetirom. Resmetirom was approved in March of 2024. It's indicated for the treatment of adults with MASLD and MASH with moderate to advanced liver fibrosis, so stage 2 to 3 fibrosis, and it's to be used in conjunction with diet and exercise. The big trial that led to the approval of resmetirom was the phase III trial with the MAESTRO MASH trial, and they looked at MASH resolution and improvement in fibrosis and found that patients on resmetirom had higher rates of MASH resolution with no worsening of fibrosis compared to placebo and greater rates of at least one-stage fibrosis improvement with no worsening in the MASLD activity score, again compared to placebo. This was the first drug we had available for treatment of patients with MASLD and MASH, and then in August of 2025 we had semaglutide getting FDA approval for patients with MASH. Again, similarly, it's approved for adult patients with non-cirrhotic MASH with moderate to advanced liver fibrosis and to be used in conjunction with diet and exercise. And the phase III trial that led to the approval for semaglutide was the ESSENCE trial, and during that trial they found that a greater proportion achieved a reduction in liver fibrosis with no worsening of steatohepatitis compared to placebo. So, those are the two medications that we have approved, but know MASLD and MASH, and we're alluding to this with diabetes and comorbidities, obesity etc., is really a metabolic disease and very closely related to other metabolic processes and that holds true for pharmacotherapy as well. So, there are multiple medications that have been studied that have liver and cardiorenal effects, particularly the glucose-lowering medications. Do you ever make recommendations to use specific medications for diabetes?

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Yes. I think if I have a patient, to be honest with you, most patients who come when they come to see us, at least in my practice for consideration of treatment of MASH, they already order a GLP-1 or a supra-agonist for treatment of diabetes or obesity. To me, it's really to consider something else. I think there are some patients who may not have approval for treatment for use of a GLP or a supra-agonist for treatment of obesity that now can qualify because semaglutide is approved. So, for treatment of diabetes, I mean going back to the ADA's guidance, the recommendation is you can use a lot of things for patients with early disease. You have probably a lot more options, and for patients with very advanced disease, like decomposed cirrhosis, you really only have

insulin, but for someone like this for treatment of diabetes, you can use a GLP-1 or supra-agonist, dual agonist, or pioglitazone.

Although a lot of hepatologists have stayed away from pioglitazone, I don't see why, but for someone like this, I think the choice of treatment of semaglutide, or we're using semaglutide as treatment of choice, to me is really a no-brainer, and the reason is that it has shown to improve cardiovascular outcomes, kidney outcomes, and heart failure. There is evidence and approval for treatment of steatohepatitis, so the risk is of hypoglycemia is pretty low. If you have to use something else because a patient can't tolerate it or any GLP-1s, then you can use other drugs. You can certainly use pioglitazone or sodium-glucose cotransporter 2 (SGL2) inhibitors. I probably would prefer those than the other drugs in this context, but of course that patient has to be on treatment with resmetirom. An F3 patient cannot wait for whether these other drugs should have evidence. Now, pioglitazone as you know, there have been some studies, small studies, and there is meta-analysis of these small studies suggesting potential benefit.

But if you want to go for an FDA-approved drug, then we have Resmetirom semaglutide. Pioglitazone is very cheap, but I think semaglutide and resmetirom are the ones that are recommended by all the guidance and guidelines, at least the liver guidelines and guidance for treatment of steatohepatitis. If someone is on tirzepatide for treatment of MASH or treatment of type 2 diabetes, then would I actually change that? Probably not if the patient is tolerating because I know there are phase II clinical trials suggesting tirzepatide would be good for steatohepatitis, but it's not approved yet. But I think we certainly have resmetirom to add to that patient's regimen. I think the choice would be based on the stage of liver disease, based on what the patient can tolerate, and what the insurance covers. We have a good number of options. I would stay away from metformin, not because I think metformin is terrible, I don't think it is. I would not use sulfonylurea in this context, and insulin I only really reserve for patients with decompensated cirrhosis because that's the only one that you can use.

Sonal Kumar, MD, MPH:

Yes. How do you feel about the SGLT2 inhibitors? Are those your go-to after semaglutide or a GLP-1?

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Yes. I think there is significant cardiovascular and kidney benefit, especially in the cardiovascular site. That's the number one cause of death in patients with MASLD. However, it's important to remember that that's for all patients with MASLD. If you get to a patient like this patient, it's not cardiovascular mortality that's the number one cause of death. It's liver mortality as number one cause of death. There is some early suggestion that this may also have benefit on the liver side, some non-invasive tests, especially hepatic steatosis. So, if I don't have other options I will use SGLT2s but knowing that there will be some sort of extrahepatic benefits as long as I can use resmetirom for that patient because also that's the drug of choice for a situation like this.

Sonal Kumar, MD, MPH:

Yes, I mean it makes it a lot easier now that we have resmetirom approved, that we can use some of these other pharmacotherapies that then add on resmetirom for more liver-directed therapy. Exactly. Especially in the patients with more advanced disease.

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

I agree completely. What do you use, Sonal, in terms of what's your choice treating? Do you treat all patients with MASH and diabetes with a GLP-1 and the supra-agonist? How do you manage lipidemia? Do you use a combination of things? Do you use statins? Do you worry about statins?

Sonal Kumar, MD, MPH:

I mean, now with semaglutide having the MASH indication, that's sort of become our go-to. But, like I said, a lot of these patients already come in on a GLP-1 by the time they come into our clinic, or if they're not on a GLP-1 there's a reason why they're not on it. But you always have the handful of patients, like this patient in this scenario, whose diabetes isn't properly controlled and then the GLP1s dual. Agonists are definitely my go-to for that. I have some people who don't tolerate a lot of medications or insurance issues for whatever reasons. And I have a few who are still on pioglitazone and they tend to do okay on it. But now with resmetirom being approved, I just add on resmetirom for that liver-directed care if for some reason they need the pioglitazone. As far as dyslipidemia, I am a huge proponent of using statins in patients. There are a lot of data that show that they're safe for people, even in cirrhosis. The only patients I'm really cautious about are those who have more decompensated disease and those need to be closely monitored, low-dose statin, things like that. But otherwise I don't really have a problem with using statins in these patients.

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

I think that's wise, and I think that's what we do as well. And the other thing, of course, that is important is that there is now more and more evidence that hypertension is actually another predictor of bad outcome in these patients. So, managing hypertension would be really important in this context. Is that what you also pay attention to more and more these days? Yes, absolutely. Let me ask you another question. I think that's not specifically for, or it could be related to the treatment. Do you rule out historical alcohol consumption is very, very poor? People underreport or they just forget, or they just don't want to talk about alcohol, and now we're using more and more positron emission tomography (PET) testing, which is a test to sort of…a biomarker for recent alcohol use. Do you use PET testing for all your patients with MASH and what is your cutoff? What kind of do you say, okay, well this patient has materiality and then what do you do then?

Sonal Kumar, MD, MPH:

Yes, so, that's a little bit tricky. I mean the first question's easier. Yes, we do test path every time a patient comes in if they consume alcohol, and usually even if they say no I will do a one-time path level because I have uncovered people who, even despite saying no alcohol consumption, they have a positive PET level. So, I at least do a one-time test, and then if it's elevated I will follow it over time. But then it's hard to decide what path level do I say "Okay, this is probably alcohol more than anything." I kind of take in the whole history because patients with uncontrolled diabetes, severe obesity, et cetera, are at higher risk for MASLD complications even if they have met alcohol-associated liver disease (ALD). And I tend to still treat them based on their cardiometabolic comorbidities. And we have providers within our clinic. We actually have a multidisciplinary alcohol clinic as well, the Center for Alcohol and Liver Medicine (CALM) clinic here at Cornell. Sometimes patients will follow in my clinic and in the CALM clinic simultaneously to help, and there are some data on the GLP-1s that they do

reduce alcohol cravings. So, I think that can be helpful. I think the patients that I tend not to treat, if it's pure alcohol use disorder, then they go on to our alcohol clinic instead.

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Yes, I think that's very really important. I think it also illustrates the fact that that the metabolic dysfunction-associated and alcohol-associated liver disease (metALD) is just part of this dynamic spectrum. I call it a dynamic spectrum because these patients can move back and forth, because people can actually drink and stop drinking, binge drink and then stop drinking, or improve their diabetes, or lose weight, gain weight. This is not a static situation, so you have to be ready to adjust it. The good news is that there are data on this where the efficacy was not impacted when you look at ALD sort of analysis. Pure alcohol associated with disease is extremely rare in the United States because when you look at patients with ALD, 90% of them have at least one cardiometabolic risk, at least one. Either it's because cardiometabolic risk factors are so common in this country or in the world, or alcohol causes obesity, causes dyslipidemia, and induces all these metabolic abnormalities.

So, finding pure ALD. Usually the pure ALD are younger patients and they have alcoholic or alcohol-associated hepatitis. And you're right, they should be treated differently, but most of the other ones should have sort of a plan to address their metabolic abnormality. Now, if there is actually alcohol-associated liver disease and they stop alcohol, some of the metabolic abnormality, they could lose weight, they could actually improve their dyslipidemia. So, there is not an urgency to address it, but I wouldn't forget about the fact that these patients may actually be treated and metALD. If I'm patient with metALD, which is a moderate amount of alcohol consumption and they have a cardiometabolic risk, I have no problem using one of the two approved drugs at this point. I know it's approved only for MASH with significant or advanced fibrosis, but to me those patients still need to be treated. I would address the alcohol consumption at the same time. I would treat not only the metabolic comorbidities but also use of a liver-targeted treatment.

Sonal Kumar, MD, MPH:

Yes, I completely agree. So, we talked a lot about pharmacotherapy and it's very exciting to have two drugs relatively newly approved, but both are approved for being used in conjunction with lifestyle recommendations, and I always talk to my patients and tell them that these medications are not a replacement for lifestyle changes and they really have to make changes to their diet and exercise. Dr. Younossi, what are you telling your patients in terms of do you talk to them about weight goals, how much to lose? There are data showing that with 5% weight reduction you start losing ketosis, 10% to improve fibrosis. Are you talking to your patients about that as well?

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Yes, I do. I think a very important concept here is how to actually communicate this information to the patient, because telling a patient to go and lose weight and come back and see you in 6 months, that's absolutely ineffective.

Sonal Kumar, MD, MPH:

That won't work.

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

You've pioneered some of these metabolic clinics. We have a multidisciplinary team, and I think that's how you have to approach it. You have to approach lifestyle recommendations the same as a prescription, meaning that you have to educate them, you have to actually provide them with goals and monitor them and bring them back, and have actually folks who are trained in this sort of treatment. So, yes, we talk about those who have obese or overweight. Ten percent weight loss is really what we hope to do, and for those who can lose the weight then they're a candidate for bariatric procedures. Certainly that's an option and, as you know, bariatric surgery. If the patients lose weight and improve diabetes, they will actually improve everything in terms of steatohepatitis, but even in those patients who have normal weight, I mean the so-called lean MASLD patients, I think I would recommend 3% to 5% body weight loss.

In terms of diet, it's not just calorie intake. Let's actually stop talking about the name of the diet. Tell them what this means, like if you're talking about the component of what is in the Mediterranean diet. That's one thing. The other thing that I actually tell them is to really stay away from ultra-processed food and also from very high-refined sugars. Those are the kind of things, beverages and things like that. Stay away from that. Alcohol. I do tell them to minimize alcohol and especially if there is any fibrosis or especially significant fibrosis, and the reason is that when you look at patients, even smaller amounts of alcohol can actually have a detrimental effect from a liver standpoint. We also know there are data on the cancer side of things but also on the liver side. So, in this situation I would recommend an alcohol sort of limitation.

Finally, exercise. I think it's important to recommend exercise, that sort of regiment that's supported by American Sports Medicine Association, 75 minutes to 150 minutes of exercise per week, but also don't forget about resistance exercise. Like I said, these patients can have sarcopenia, at least there's a theoretical that GLP-1 agonists can cause sarcopenia. So, having mood nutrition, improvement of muscle, but also exercise would be critical, and if folks are interested to go back to the global consensus recommendation that came out in *Gastroenterology* last month, there is a nice figure that you see and it's pretty easy to follow these.

Sonal Kumar, MD, MPH:

Yes, great. We talked about appropriate medications and we've talked about lifestyle modifications. Now what about the interprofessional team? This is a figure from the ADA guidelines for MASLD in people with type 2 diabetes. The care team really varies according to the risk assessment for the patient. I think this just stresses how important it is that we do appropriate risk assessment in our patients because how we intervene or who the appropriate team members are varies according to that. MASLD affect 30% of the population, but 30% of the population cannot be, unfortunately, in the hands of a hepatologist. So, we really need to select out these high-risk patients. How are you working with other team members, especially? I mean we always knew this was a metabolic disease, but now there's so much overlap with pharmacotherapy and things. How should providers coordinate or do you have any recommendations?

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Well, this figure is a beautiful figure, and I'm a member of the ADA guidance and guideline committee that was part of this. That gave a lot of credit to my colleagues and endocrinology side, and there were about three or four of us hepatologists who were part of a large group because that actually provided very good guidance on what to do for earlier patients with F0s and F1s. These patients can be managed by their primary care physicians

or endocrinologists wherever they want if they have metabolic issues, and of course lifestyle is the key. If there is actually diabetes or another component of metabolic syndrome, you want to reassess them. I would reassess those patients with just a FIB-4 in a year. If there are no cardiometabolic risks, then you can reassess them still maybe in 3 to5 years rather than just every year.

The patient who needs to be seen by hepatologists is really the cirrhotic patient, the patient who has cirrhosis, because even if you want to do a lifestyle intervention, you just have to be careful not to cause some nutritional issues for these patients and worsen their sarcopenia, and that is critical. And then make sure to screen those patients for papillary carcinoma, at high risk for that, and also when the need is for liver transplantation to make sure that they're in the transplant setting. In the middle group, which is basically these patients with moderate to some advanced amount of fibrosis, this is where the multidisciplinary team would be absolutely critical. You need to have a hepatologist, or their advanced practice provider (APP), but what if this is done within a single center, which I think is what you have experienced, or you could put this in sort of a virtual where you have components of this sort of multidisciplinary team coming together, I think would be critical.

And I'm a believer that hepatologists should be involved where they need to be involved of course in all of these things, but our APPs need to be involved in every step and that means APPs from GI and hepatology, APPs from endocrinology, and even actually in the primary care setting. When we bring this together, I think it would work very well. My challenge and our challenge is that there is not a lot of coverage for things like behavioral health or exercise or nutrition assessment and consultation. So, the health system that's a part of it would consider that as a part of a package of how to actually improve the outcomes of these patients. They would have to actually consider that because, at the end of the day, if you actually prevent a patient death or cirrhosis, because the cost of taking care of patient with decomposed cirrhosis is so much, then that will be a big win for the system. I think these are the kinds of things that we need to teach our administrators, that this is actually a package that if you have to provide some behavioral health as expertise and provide support for that, you get actually much better outcomes. And what I call these sorts of settings is metabolic clinics, so that the patients come in, they get their eye exam for diabetes retinopathy, their clear heart assessment, their liver assessment of the FIB-4, and then the idea appropriately followed up and connected to the right specialist.

Sonal Kumar, MD, MPH:

Yes, I completely agree. I mean, I am really interested in multidisciplinary care for these patients, and I think one of the nice things with having pharmacotherapy that's been approved now is that there's a lot more disease awareness and a lot more recognition among other providers in primary care in endocrinology that MASLD is really a metabolic disease and there is a benefit in care coordination, but I agree that there is not enough support for dietary, nutritional counseling, behavioral health, things like that, which are equally important to having pharmacotherapy options, and there's so much overlap now that I think I agree with you, there should just be a metabolic clinic where they can sort of have a one-stop shop and get their appropriate diseases managed.

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Sonal, you've had good experience with this kind of metabolic clinic. Just tell us a little bit about the patient's perspective. I would assume they would love this because, as we were transplant pathologists, a transplant sort of care coordination where you've got everybody in the same sort of clinic, has always been very positive for

patients. So, tell us a little bit about how patients actually feel about coming together and seeing everybody. That matters.

Sonal Kumar, MD, MPH:

Yes, I mean, they love it. It really reduces care fragmentation. We have an endocrinologist, cardiologist, and hepatologist and we actually have dieticians as well and they don't see everybody on the same day unless they need to, but it's really nice, especially when it comes to management of comorbidities, the discussions about whether the statin is safe or not. You can make the decision right then and there because the endocrinologist is sitting right next to you, or whether or not we need to add resmetirom because they're not tolerating their GLP-1 and they have no advanced fibrosis, or if you're thinking about starting a medication to have discussions with it. Patients love it. It is a little bit longer of a visit, but they have back-to-back visits and then they are able to have a very cohesive care plan when they leave clinic that day as opposed to me saying, "Okay, let me reach out to your endocrinologist, we'll talk, we'll see what happens." And then there's a lot of back and forth and there's this uncertainty in the patient's mind of what the next step is. I think it's really helpful for them to know that we're all on the same page.

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Yes, and I think it's really important. I think one other point that I'd also want to make is that some of us say the care should solve with primary care. Of course primary care has to be engaged and involved in everything that we do because that's really a lot of patients with diabetes. Most patients with diabetes are cared for by primary care. I think they should be a part of all of this. I have to say that this table was actually created with a lot of input from some fantastic primary care providers who are actually part of the committee, but I think this will give you at least a structure of where somebody should be responsible for the part of this understanding that primary care physicians, in the United States at least, are extremely busy. They don't have time, so we have to come together and make it easy for them.

Take those patients who really can still be engaged and involved, but cirrhotic patients who have decompensation probably should be managed by a hepatologist and hepatology team, but it doesn't mean that you should exclude the endocrinologist or a primary care physician, because there are so many other comorbidities and they are so much more well-trained than we are. I think this concept of the metabolic clinic and considering this disease as a part of the galaxy of different metabolic diseases together, I think is really critical in how we sort of change our perspective, because how we were trained as gastroenterologists and hepatologists, we all had these boxes and these lines that they didn't want to cross. Well, for this disease you have to cross them because if you don't cross them then you don't actually serve the patient the best stuff that you can do.

Sonal Kumar, MD, MPH:

Absolutely.

That's about all we have for today. Any final thoughts or anything else you'd like to discuss, Dr. Younossi?

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

I think the only thing I would say is that it probably would be important to remember that more and more hepatologists and gastroenterologists are staying away from liver biopsy. Even I think in a few years clinical trials will not require a liver biopsy. Liver biopsy was good at the time, but we are getting better and better in non-invasive tests and I think would be good. And the one last question I have for you, Sonal, is, Do you expect, not just as what we're currently doing is putting patients on a GLP-1 or supra-agonist and we add resmetirom, are you expecting the combination of two or three drugs, resmetirom, semaglutide, or maybe a third drug that's going to be approved as sort of the future? And if you have that or you can have that patient treated with two or three drugs, which costs a significant amount of money for a year or forever, how do you stop?

Sonal Kumar, MD, MPH:

These are all great questions. I think when it comes to combination therapy we have to think of MASLD as any other metabolic disease and sometimes patients do require multiple treatment options. If you look at diabetes, if you look at hypertension, patients sometimes are on multiple drugs and someone may have a partial response with one drug and then you need additive therapy. So, I think combo is going to be in the future and we're seeing it already. There are people who are on GLP-1s who are using resmetirom, even in the MAESTRO-NASH trial, where 14% of patients were on a GLP-1. It wasn't approved for MASH at that point, but we've seen some patients on combination. So, I think we have to keep that in our toolbox. That is a possibility, especially in the patients we think have more advanced disease because we really do not want those patients to progress.

We do not want them to develop cirrhosis, we don't want them to have decompensated disease, liver cancer, etc. So, absolutely. Now, the question of what do we do if they respond or when do you stop the medication? Same thing. This is a chronic metabolic disease and just like you don't really stop anti-hypertension, you don't stop glucose-lowering therapy. I don't think right now I can confidently recommend stopping resmetirom or semaglutide when it's being used for the treatment of MASH. There is something that led to this disease progression and they would be at risk for getting it again, but I do hope that the cost goes down, and so as more and more drugs do become available, I'm hoping that goes down and it's a little more feasible to use multiple medications, keep them on the drug.

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

I completely agree. I think combination is the future. I have sort of this feeling that we will have to treat probably for a year with probably multiple medications and we all try to actually minimize medication at some point and polypharmacy. So, you could consider our sort of dropping certain things, especially those that have side effects, off the list and see how can you maintain response with a minimum amount of medication that can be used, and I think that's something we need to see in the future. And the only other thing that I would have to just add to this is that currently the drugs are approved based on the surrogate of outcome, which is fibrosis and steatohepatitis resolution. We all are going to have to show that these drugs will improve outcome. They're going to reduce more cirrhosis, they're going to reduce more mortality, they're going to reduce hepatocellular carcinoma (HCC) cases.

Those data are not out there, but they're going to come. And I have looking at cardiovascular benefit of some of the GLP-1 and receptor agonists many years later because these guys in cardiology do very large clinical trials. We have seen actually cardiovascular benefit, kidney benefit, and I'm hoping and I'm positive that we will see

liver outcomes benefit in time, and I think both of these two drugs that we have available really opened this field for us where we did not have anything. I think this is really a fantastic time for us because people ask me, "Well, which drug is better than the other one?" Listen, I'm very happy that our patients have now two choices because over a year ago I had no choice. And talking about resmetirom or semaglutide raises awareness to everyone, and I think it's good for patients, good for providers, and ultimately maybe we will at least make a dent in this sort of global epidemic starting with lifestyle and also with these drugs.

Sonal Kumar, MD, MPH:

Absolutely, and on that note, I'd just like to thank you, Dr. Younossi. It's always a pleasure to speak with you, and thank you for your expert perspectives on the treatments that we have for MASLD and MASH. And thank you to our audience for participating. Before we close, I have just two SMART goals, which are specific, measurable, attainable, relevant, and timely action items that you can hopefully apply to the care of your patients in your own practice. Within the next 3 months, increase lifestyle counseling including nutrition, weight management, and physical activity in combination with pharmacotherapy when appropriate for patients with or at risk for MASLD and MASH, and then number two, implement FDA-approved therapies with either resmetirom and/or semaglutide, when relevant, in appropriate patients with MASLD or MASH.

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Well, thank you very much, Sonal, for including me. This was wonderful.

Sonal Kumar, MD, MPH:

Thank you so much, and then one final thing, to receive credit for this activity, please complete the evaluation and post-test online, and, again, please check out the other three snack activities in this series. Thank you and have a good day.

Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD:

Thank you.

