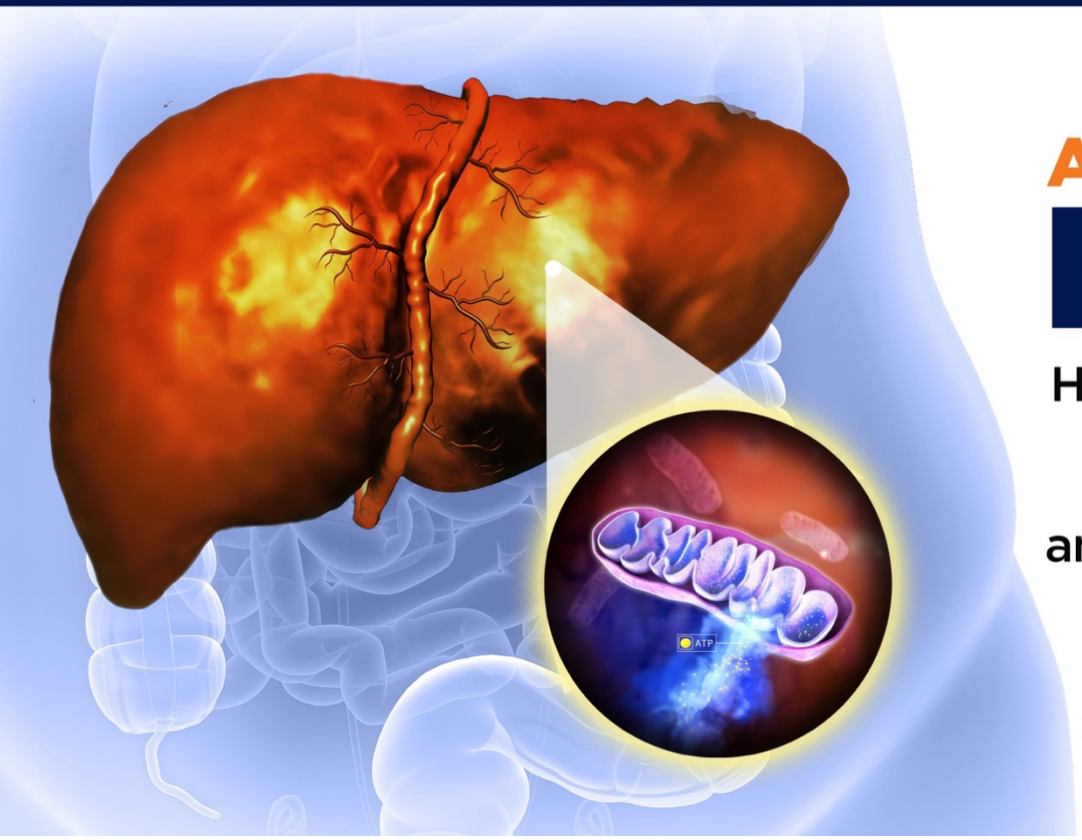

A NEW ERA IN MASH

How Disease-Specific Therapies Are Changing the Game and Best Practices for Clinical Integration

Frequently Asked Questions

Expert consensus recommendations for treatment with resmetirom indicate that treatment may be considered with a vibration-controlled transient elastography (VCTE) measurement of 15.1 to 19.9 kPa. When is it better to treat patients whose VCTE is closer to 15 kPa vs 20 kPa?

Metabolic dysfunction-associated steatohepatitis (MASH) is a disease in which obesity is prevalent and because of that, there is less reliability in liver stiffness measurements. It is important to look at multiple tests in aggregate when deciding whether to treat with resmetirom since some tests may be less accurate in measuring fibrosis. In patients with a VCTE of 20 kPa or higher, there is greater likelihood of clinically significant portal hypertension and treatment is not recommended for those patients. Even with liver biopsy, inaccuracies may occur with pathology interpretations and therefore multiple noninvasive tests (NITs) should be used to ascertain the patient's clinical status.

Is there any evidence that prothrombotic factors (eg, von Willebrand factor) are involved in the progression of MASH and its associated complications?

Multiple studies suggest a relationship between metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic risk factors and a hypercoagulable state, though prothrombotic factors are not established predictors of MASH outcomes and

require further investigation. At the present time, fibrosis stage is the most important predictor of liver-related outcomes. Noninvasive assessments of liver fibrosis that predict liver decompensation include an enhanced liver fibrosis (ELF) test score of more than 11.3, a VCTE of 30 kPa or higher, or a magnetic resonance elastography (MRE) of 6.48 or higher. It is important to observe longitudinal changes over time to determine whether a patient is experiencing rapid or slow fibrotic progression to inform treatment decision-making.

A significant number of patients treated with resmetirom during the 52-week MAESTRO-NASH clinical trial did not experience improvement in fibrosis. Is there value in preventing progression, but not fibrosis improvement, in patients with MASH?

The development of fibrosis usually occurs over a period of time that is longer than the initial 52-week study period of MAESTRO-NASH. Thus, these patients may need to be followed for longer than the initial study period to see whether more patients experience fibrosis improvement. The MAESTRO-NASH study is ongoing for 54 months to observe whether further improvement occurs or progression to cirrhosis, which will be an important outcome. There were also additional effects, such as improvements in NIT results and lowering of low-density lipoprotein cholesterol (LDL-C), which shows there are benefits to patients even if fibrosis is halted but not improved.

Would you treat a patient with resmetirom if they had cirrhosis?

There is not yet enough safety data from MAESTRO-NASH to support the treatment of cirrhosis with resmetirom, and therefore these patients should not be treated with it. Patients with cirrhosis are being evaluated to see whether they can be safely treated with resmetirom, but the data are not yet available.

Is there a platelet count that would be considered too low for the patient to undergo treatment?

Consider the longitudinal results of a patient's platelet count. If one test is abnormally low, this may be the result of a transient condition, such as a viral illness. However, if a patient has consistent low platelet counts (<140 k/μL) and evidence of portal hypertension, they should not be treated.

Is the antifibrotic effect of resmetirom liver specific or does it reduce fibrosis in other organs affected by metabolic dysfunction?

The antifibrotic effect of resmetirom has been evaluated in the liver, but we do not have direct proof of reductions in fibrosis in other organs, such as the kidneys and heart. Resmetirom does reduce LDL-C along with other atherogenic lipids and lipoproteins. Over time, data eventually may show improvements in cardiovascular outcomes and other organs affected by metabolic dysregulation.

How would you manage a patient with a diagnosis of hepatosplenomegaly that was an incidental finding on an ultrasound, but whose liver function tests (LFTs) were normal?

A good rule-of-thumb is if the spleen is more than 14 cm long, then the patient should undergo further evaluation. If a patient has a spleen size of 12 cm, but the splenomegaly is only supported by a radiologic finding, the patient may not have cirrhosis based on findings from other NITs. The overall clinical picture is what matters most so consider other tests, such as VCTE, ELF score, MRE, and platelet counts, when deciding whether to treat a patient.

In a patient with splenomegaly, low platelets, and a hepatic venous pressure gradient (HVPG) of 6 mm Hg, would you perform an esophagogastroduodenoscopy (EGD) to determine if the patient had varices?

In a patient with an HVPG that is lower than expected, an EGD would be appropriate to screen for varices. Of note, patients with MASH may have lower levels of clinically significant portal hypertension.

Were patients who drank alcohol excluded from the MAESTRO-NASH trial? How was alcohol use monitored during the trial?

A questionnaire and patient reporting were the only screening tools used to assess alcohol consumption during MAESTRO-NASH. In the MAESTRO-NASH-OUTCOMES trial, patients are screened with phosphatidylethanol (PEth) testing, and a negative result was required to be enrolled in the trial. There will be categories of patients who were not included in the MAESTRO-NASH study, such as patients with HIV or hepatitis B, where clinical judgement is necessary to decide whether to treat since clinical studies in certain patient populations are unlikely.

What is the cost of resmetirom?

The cost is approximately $45,000 per year. However, many insurance plans are providing coverage. Providers and patients also should research rebate programs and programs for uninsured patients to help with medication costs.

What is your approach to helping patients make lifestyle changes?

This is one of the most difficult points in clinical practice because most patients have been on a diet for decades. They usually have seen a dietitian or other specialists. Encourage patients to change their lifestyle instead of focusing on losing weight. Patients should incorporate easy changes, such as eliminating fructose-containing beverages—they should drink water or seltzer—and exercise that includes both

moderate aerobic activity and resistance training. Increasing muscle mass is important for improving lipid metabolism and insulin sensitivity. Also, maintaining muscle mass is important for patients are who are taking a glucagon-like peptide-1 receptor agonist (GLP-1RA).

Who else do you involve when recommending lifestyle interventions to patients?

Working closely with a dietitian is recommended if those services are available. Lifestyle interventions, such as diet and exercise, are one of the most important aspects of disease management since they can impact patient health at any stage of disease. Exercise in the absence of weight loss can provide health benefits by improving cardiovascular health and decreasing all-cause mortality.

Many patients have tried dieting with little success and working with a professional may help patients achieve their goals. Notably, the MAESTRO-NASH trial showed that weight loss of as little as 5% can improve the efficacy of resmetirom. There are online programs that provide consultation with a dietician, and clinicians should provide patients with information on those available resources.

What is your opinion on moderate alcohol consumption?

Patients with any degree of fibrosis should abstain from alcohol consumption. In patients who have consistently shown to have a lack of fibrosis over time, it becomes a quality-of-life issue where moderate alcohol consumption may be considered on an individual basis.

How do you evaluate alcohol consumption in your patients?

PEth testing should be performed in all patients as part of routine evaluations. Values can be followed over time to determine whether recommendations to decrease alcohol consumption are being followed. However, the sensitivity and specificity of PEth testing must be considered like any other NIT and values may be less accurate in patients who are not consuming high volumes of alcohol. Also, it is important to remember that resmetirom is approved in the United States for treatment of MASLD and not metabolic dysfunction and alcohol-associated liver disease. In the MAESTRO clinical trial, patients were included if alcohol consumption was less than 20 g/day for women or 30 g/day for men.

Would you treat a patient with alcoholic liver disease with resmetirom?

Resmetirom was not studied in a population with alcoholic liver disease. If a patient is reporting a significant amount of alcohol consumption, they should cut down on their alcohol use. Resmetirom therapy can then be considered later if their alcohol use

continues to be within an acceptable range. In the future, it will be important to study resmetirom in a population with significant alcohol use to determine the efficacy and safety of treatment.

What are your thoughts about using shear wave elastography to assess liver stiffness, which is less operator dependent and evaluates more areas of the liver, rather than FibroScan?

There is currently a high degree of variability with the use of shear wave elastography. However, as the data become more standardized, shear wave elastography will be a useful tool for providers.

Would you start treatment with a GLP-1RA in patients with chronic liver disease that is classified as F1 or F2?

Yes, it is reasonable to treat the metabolic dysfunction first and see whether the patient's outcomes improve. However, more liver-directed therapies are needed as fibrosis increases.

Which drugs interact with resmetirom?

Clopidogrel is one of the main drugs that interacts with resmetirom. Patients taking clopidogrel must use a lower dose of resmetirom. Also, resmetirom is contraindicated in patients who are taking cyclosporine or gemfibrozil.

How should you manage patients with cirrhosis with no established diagnosis of MASH?

Patients can present with burnt-out MASH or cryptogenic cirrhosis. The natural history tends to be more aggressive than patients with evidence of steatosis or cirrhosis. These patients need to be enrolled in clinical trials studying the treatment of cirrhosis since their disease progression and liver composition are different than more typical patients with MASH. Fibrosis-4 (FIB-4) scores should be calculated regularly in patients with a history of diabetes to help identify patients with MASLD/MASH earlier in the disease progression when treatment can be effective.

Are FibroSure test scores equivalent to the FIB-4 scores that were presented for stages F1 and F2?

FibroSure is an older test that was developed in patients with hepatitis C virus (HCV). FIB-4 (also originally studied in HIV/HCV) and the additional NITs we discussed today have been more extensively validated in an MASLD/MASH population. Therefore, more recent tests should be used if available. Overall, consider the entire patient (eg, comorbidities, age, and LFTs) when diagnosing a patient with MASLD/MASH.

Be aware that several factors can also affect FibroScan test results. First is body mass index (BMI). Be careful of false-positive results in patients who have a BMI above 40 kg/m^2. Second, very high LFTs can overestimate the fibrosis stages. FibroScan testing is not recommended in patients with alanine transaminase (ALT) levels greater than 200 IU/L. Be cautious with using FibroScan in patients with ALT values greater than 150 IU/L. Finally, congestive heart failure can result in a false elevation in liver stiffness. Liver stiffness is a surrogate marker of liver fibrosis and can be affected by blood flow and inflammation in the liver.

Also, realize that a FIB-4 score cutoff value of 1.3 is helpful for ruling out patients who do not have MASLD/MASH since it has a very good negative predictive value. However, it is not as good at positively identifying patients. Some patients with diabetes may have FIB-4 scores of 1.1 or 1.2, and other NITs should be included when determining whether these patients have MASLD/MASH. Finally, age is also a consideration for diagnosis. A FIB-4 cutoff value of 2.0 is suggested for individuals older than 65 years to limit false-positive results.

Are there plans to use resmetirom to treat adolescent patients with obesity and MASLD?

Resmetirom is currently approved only for the treatment of adults with nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (F2 to F3). There will be a study evaluating the efficacy and safety of resmetirom is adolescent populations in the future.

There is a large burden of disease in patients with Hispanic ethnicity who receive Medicare or Medicaid benefits or are uninsured. We know that GLP-1RAs are not approved by Medicare and Medicaid, but will resmetirom be approved for use?

Dr. Alkhouri recommends prescribing resmetirom for patients who are appropriate for treatment and receive Medicaid benefits. He believes the medication is likely to be approved. Individuals with commercial insurance and Medicare should have coverage for resmetirom.

How should you assess patients with obesity for liver cirrhosis to determine if they are candidates for treatment with resmetirom?

Patients should be rigorously tested for portal hypertension, including undergoing endoscopy. Patients with obesity should also be assessed with MRE to more accurately stratify the risk of fibrosis since VCTE can be less reliable in this patient population.

Did hypothyroidism affect outcomes of patients in the resmetirom group in the MAESTRO-NASH clinical trial?

No, patients enrolled in MAESTRO-NASH who had comorbid hypothyroidism needed to have controlled disease—in other words be on a stable dose of levothyroxine and have a normal thyroid-stimulating hormone (TSH) level prior to enrollment. Based on the data thus far, resmetirom has minimal effect on the thyroid axis because it specifically targets intrahepatic hypothyroidism. Patients do experience a decrease in thyroxine (T4), but there is no change in triiodothyronine (T3) or TSH.

Do you change your diagnostic approach to MASH in patients who have a normal BMI?

In addition to BMI, dyslipidemia, insulin resistance, and prediabetes status also should be considered when diagnosing MASH/MASLD. If a patient has any of those risk factors and a BMI of less than 25 kg/m^2, then the diagnostic and treatment approach is nearly the same as in an individual with a BMI equal to or greater than 25 kg/m^2. The only exception is that targeted weight loss should be 3% to 5% body weight with a BMI of less than 25 kg/m^2 rather than the typical 10% body weight reduction for patients with higher BMIs. If patients who are lean (BMI <25 kg/m^2) do not have any additional metabolic risk factors, they should be evaluated for other causes of metabolic liver disease, such as hypobetalipoproteinemia and lysosomal acid lipase deficiency.

Some patients have genetic variation in the *PNPLA3* gene that confers susceptibility to MASLD and may be present in patients who are lean. There is a high prevalence of the variant that increases the risk of steatotic liver disease among Hispanic and Latino patients in the United States. However, current standards of care in the United States and Europe do not include routine assessment for the variant. In patients who are lean with suspected MASLD/MASH, a lower threshold for liver biopsy is acceptable.

Should the weight loss paradigm for MASLD/MASH shift from assessment of BMI to assessment of abdominal fat loss?

Consideration of fat distribution is important when assessing a patient's BMI. European guidelines note that visceral fat distribution confers a higher risk of MASLD. With respect to treatment, it is important to have drugs that reduce fibrosis rapidly because patients with F3 fibrosis have a 20% risk of progressing to F4 within 2 years. There may not be enough time for metabolic drugs to effectively improve the outcomes of these patients.

Combination treatment with resmetirom and semaglutide can be useful for certain patients because it is important to target fibrosis and insulin sensitivity in MASH. In patients with F3 fibrosis, resmetirom would be a good first choice because of its ability to reduce liver fibrosis. A GLP-1RA, such as semaglutide, can be added later to improve weight loss. Starting with a GLP-1RA is a better option for patients with less advanced disease (ie, F1 or F2 fibrosis). Resmetirom can be added later if there is no improvement with a GLP-1RA alone.

What is the effect of smoking on MASLD/MASH progression and response to treatment?

Smoking is associated with progression of fibrosis in patients with MASLD/MASH, and patients should be counseled to quit smoking. The effect of smoking on treatment response is not known at this time because smoking status has not been evaluated in clinical trials so far.