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NARRATIVE REVIEWS

Charles J. Kahi, Section Editor

Expert Panel Recommendations: Practical Clinical Applications for Initiating and Monitoring Resmetirom in Patients With MASH/NASH and Moderate to Noncirrhotic Advanced Fibrosis

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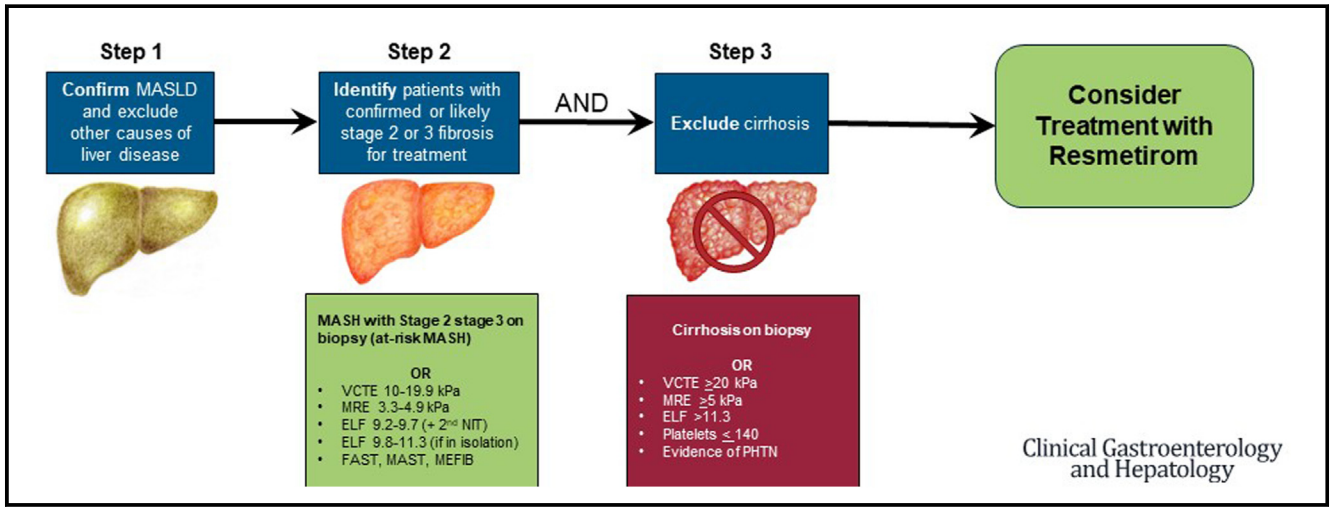

Metabolic dysfunction–associated steatotic liver disease affects 1 in 4 people in the United States and western Europe, with an important proportion developing metabolic dysfunction–associated steatohepatitis (MASH), the progressive subtype of metabolic dysfunction–associated steatotic liver disease. Cirrhosis caused by MASH is a leading indication for liver transplantation and the most common cause of hepatocellular carcinoma. Hitherto, there have been no specific pharmacotherapies for MASH. The recent conditional approval by the Food and Drug Administration of resmetirom for the treatment of moderate or advanced MASH presents a much-anticipated therapeutic option for patients with noncirrhotic advanced MASH. Specifically, the intended population for resmetirom are patients with MASH and fibrosis stages 2 or 3. The approval of resmetirom also presents important challenges, including how to noninvasively identify patients with fibrosis stages 2–3, and how to exclude patients with more advanced disease who should not be treated until further data emerge on the use of resmetirom in this population. Herein we consider the available literature with regard to identifying the intended population for treatment with resmetirom and in proposing criteria for stopping treatment.

Keywords: NASH; MASH; MASLD; FDA; Approved Drug.

On March 14, 2024, the Food and Drug Administration (FDA) announced the conditional approval of resmetirom for the treatment of fibrotic (stage 2 or 3) metabolic dysfunction–associated

Abbreviations used in this paper: **AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; CAP, controlled attenuation parameter; FDA, Food and Drug Administration; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; LSM, liver stiffness measurement; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NASH, nonalcoholic steatohepatitis; NIT, noninvasive tests; PDFF, proton density fat fraction; VCTE, vibration controlled transient elastography.**

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steatohepatitis (MASH), the progressive subtype of metabolic dysfunction–associated steatotic liver disease (MASLD).[1] Until now, conditional FDA approval for a drug to treat MASH has been elusive, despite numerous trials reaching advanced phases of development.[2–6] Full FDA approval is considered when a drug demonstrates that it favorably impacts clinical outcomes in patients with MASH. Because it can take an extensive period of time to achieve this, in the context of noncirrhotic MASH with moderate to advanced fibrosis (stage 2 or stage 3), conditional approval can be granted by the FDA after prespecified histologic end points are met, namely, resolution of steatohepatitis, without worsening of fibrosis, or a 1 stage improvement in fibrosis without worsening of steatohepatitis.[7]

The approval of resmetirom to treat patients with moderate to advanced fibrosis without cirrhosis is a landmark achievement in the field of MASH after more than 2 decades of research. It is currently the only liver-directed therapy with supportive phase 3 data stemming from successful completion of the first part of the MAESTRO NASH phase 3 trial.[1] The FDA's initial approval for resmetirom states that resmetirom "is indicated in conjunction with diet and exercise for adults for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) (MASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis)." The label excludes patients with cirrhosis and those with early (F0-1) fibrosis. The intended potential treatment population is thus synonymous with that referred to in the literature as "MASH with significant fibrosis," "MASH and moderate fibrosis," or "at-risk MASH." The latter is identified in the most recent American Association for the Study of Liver Diseases (AASLD) guidance as the population most likely to benefit from a treatment intervention.[8] Here, we use the term at-risk-MASH, to describe the patient population studied in the MAESTRO-NASH trial. Using data from the trial, in addition to benchmarks set forth in the published literature, we provide guidance on the identification of at-risk MASH patients who may benefit from initiating treatment with resmetirom, along with recommendations for the assessment of treatment response. Some cutoffs recommended in this document may diverge slightly from what has been published in prior guidances,[8] because data from this trial and the FDA analysis were prioritized to maximize relevance and applicability to patients being considered for resmetirom therapy. In patients meeting criteria for treatment, the FDA label recommends weight-based dosing with 80 mg designated for patients <100 kg and 100 mg for those >100 kg body weight. Because this document was written in the initial phases post-drug approval, further analysis of emerging data, including real-world evidence, particularly regarding monitoring of therapeutic response, are likely to further guide best practice in the coming years.

What You Need to Know

Background

Resmetirom is the first liver-specific drug to receive conditional approval in the U.S. by the FDA for the treatment of patients with non-cirrhotic MASH consistent with fibrosis stage 2 or 3 (F2-3).

Findings

The FDA label does not require the use of liver biopsy. We use data from the MASTERO-NASH trial and other consortia to select cut-offs for non-invasive tests (NITs) to identify F2 and F3 fibrosis to initiate and monitor therapeutic response.

Implications for patient care

This expert panel review allows clinicians to use a variety of NITs to start and monitor resmetirom therapy.

Selection of the Target Treatment Population

Diagnosis of Metabolic Dysfunction–Associated Steatotic Liver Disease

MASLD is a highly prevalent condition that can coexist with other causes of liver disease that should be considered as part of an initial evaluation of patients suspected of having MASH.[8] In selecting the appropriate patient for resmetirom, a diagnosis of MASLD must first be made. Although this trial was designed and enrolled before the nomenclature change, the overlap between the old and new nomenclature was 99%. Other clinical research datasets have shown similar results, concluding that the definitions in this setting identify the same patients, as outlined in the nomenclature change compendium to the AASLD nonalcoholic fatty liver disease guidance.[9,10] Given the high prevalence of MASLD, the presence of other concomitant etiologies of liver disease should be considered. The most common additional diseases to consider are alcohol-associated liver disease, iron overload, viral hepatitis, and autoimmune hepatitis. Thus, before the initiation of treatment, other causes of liver disease need to be excluded, as indicated in the AASLD guidance document.[8] We strongly suggest ruling out autoimmune liver disease because several MASH trials have inadvertently included these cases, leading to subsequent concerns about elevated liver enzymes within these trials. If autoimmune liver disease is suspected, such as might be the case with high titer antinuclear antibody or anti–smooth muscle antibody positivity, additional testing should be pursued (eg, quantitative immune globulins and possibly, a liver biopsy, depending on clinical suspicion). Alcohol intake should be assessed by history excluding those exceeding the allowed amount for MASLD/MASH diagnosis and, ideally,

biomarkers (eg, phosphatidylethanol) if there is clinical suspicion, given alcohol intake is often underreported.[11]

Histologically Diagnosed Stage 2-3 Fibrosis

Liver biopsy remains a potentially important diagnostic option, particularly in instances of discordance between noninvasive tests (NITs). However, studies have demonstrated that using multiple NITs can increase precision for staging hepatic fibrosis and predict clinical outcomes.[12–14] Importantly, if a historical liver biopsy within 12 months indicates MASH with stage 2 or stage 3, resmetirom may be considered irrespective of NIT values, other than if there is clinical or imaging evidence of portal hypertension. In the setting of an older historical biopsy (up to 3 years), the same concept should be applied to avoid treatment of those with evident cirrhosis. If NITs suggest minimal fibrosis (as would be in the setting of disease improvement), a repeat liver biopsy could be considered. Nonetheless, baseline NITs should be acquired to monitor treatment response.

In the absence of a biopsy confirming MASH with stage 2 or stage 3 fibrosis, we propose using several noninvasive criteria, depending on their availability in individual practice settings, preferably liver stiffness measurement (LSM) by vibration controlled transient elastography (VCTE; and/or magnetic resonance elastography [MRE], where available), based on MAESTRO-NASH and current AASLD guidelines (Tables 1 and 2).[8]

Noninvasive Assessment of At-Risk Metabolic Dysfunction–Associated Steatohepatitis

Patients with "at risk" MASH, those with histologic evidence of steatohepatitis in the presence of stage 2 fibrosis or higher, are at significantly increased risk of liver-related morbidity and mortality. Fibrosis progression closely correlates with adverse hepatic outcomes, such as hepatic decompensation (ascites, hepatic encephalopathy, variceal bleeding, or hepatocellular cancer), which can result in death or the need for liver transplantation.[15] The disease spectrum includes MASL, MASH with no or early stage fibrosis (F0-F1), MASH with significant or moderate fibrosis (F2 and higher, significant liver fibrosis), MASH with advanced fibrosis (stage 3 in this context), and cirrhosis. Patients with noncirrhotic significant liver fibrosis (defined as stage 2 or 3 in this context) are more likely to have hepatic complications.

Table 1. Proposed Criteria to Identify Patients with MASH and Significant/Advanced Fibrosis

Criterion	Cutoff	Comments
1. Suggested initial tests to identify presumed MASH (after ruling out other causes of liver disease)		
FibroScan CAP	≥280 dB/m[a]	Alternative steatosis assessment options: • Quantitative assessments o MRI–proton density fat fraction ≥5%). • Qualitative assessments o CAP score ≥280 dB/m should be used with at least 1 of the parameters listed below.
AST	>17 IU/L (female) >20 IU/L (male)	Similar to inclusion criteria for MAESTRO-NASH.
2. Subsequent tests to identify the presence of significant/advanced fibrosis		
VCTE	10–15 kPa	Because of the variability of the technique, it is recommended to follow the recommended best practices, including but not limited to obtaining >10 measurements, achieving an interquartile range <30%, recommending the patient fasts for at least 3 hours before the measurement, and checking images to ensure the absence of rib echo.
VCTE	15.1–20 kPa	In the absence of laboratory, clinical, or imaging features of cirrhosis (also see patients who should not be treated with resmetirom).
ELF	9.2–10.4	ELF 9.2–9.7, an additional NIT should corroborate likely stage 2 or 3 fibrosis to reduce the risk of misclassifying patients. ELF 9.8–10.4 in the setting of MASLD may be used to identify patients for treatment with resmetirom, when TE not available. If ELF 10.5–11.3, additional caution is needed to exclude the presence of cirrhosis (eg, liver stiffness above threshold values for VCTE or MRE) (Figure 1).
MRE	3.0–4.3 kPa	If MRE 4.4–4.9, additional caution needed to exclude the presence of cirrhosis (Figure 1).

AST, aspartate aminotransferase; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NIT, noninvasive tests; TE, transient elastography; VCTE, vibration controlled transient elastography.

Table 2. Alternative Composite Tests to Identify At-Risk MASH

FAST	≥0.67	Predictivity is largely driven by AST and this cutoff may fail to identify many patients
MAST	≥0.242	As for MRE
MEFIB	FIB-4 ≥1.6 plus LSM by MRE ≥3.3 kPa	Positive MEFIB has a high PPV >90%

NOTE: In the setting of advanced fibrosis, steatosis may be lower than limit of detectability of CAP.
AST, aspartate aminotransferase; FAST, FibroScan–aspartate aminotransferase; FIB-4, Fibrosis-4; LSM, liver stiffness measurement; MASH, metabolic dysfunction–associated steatohepatitis; MAST, magnetic resonance imaging–aspartate aminotransferase; MEFIB, magnetic resonance elastography + Fibrosis-4; MRE, magnetic resonance elastography; PPV, positive predictive value.

Those with cirrhosis are at the highest risk of adverse liver-related outcomes but, because of potential differences in hepatic metabolism or tolerability, are studied separately and have a distinct guidance pathway for clinical drug development by the FDA.

Here, it is pertinent to outline the baseline characteristics of patients enrolled in the MAESTRO-NASH study (NCT03900429) alongside their corresponding NITs.[1,16] Eligible patients in the MAESTRO-NASH study had at least 3 cardiometabolic risk factors and had undergone prescreening VCTE within the past 3 months revealing a controlled attenuation parameter (CAP) of 280 dB/m or more and a LSM of 8.5 kPa or more. Additional key inclusion criteria were histologic evidence of MASH with NAFLD Activity Score ≥4 and F2, or F3 fibrosis. Per FDA label, participants with stage F2 or F3 in the study (n = 888) were 56% (542) female, and included 608 (68%) patients with type 2 diabetes mellitus, 700 (79%) with hypertension, and 6833 (71%) with dyslipidemia. Importantly, the CAP baseline median (interquartile range) was 349 (320–378) dB/m, LSM on VCTE was 12 (10–15) kPa, and enhanced liver fibrosis (ELF) score of 9.7 (9.2–10.4).[17] Interestingly, the median Fibrosis-4 (FIB-4) in MASH patients with F2 and F3 in MAESTRO-NASH was 1.3 (1.0–1.8), indicating that FIB-4 correlated less well in this setting (patients with at least 3 metabolic risk factors and VCTE revealing a CAP of 280 dB/m or more and an LSM of 8.5 kPa) than in the general population for the identification of F2 or F3 disease. Therefore, FIB-4 is not an ideal decision-making tool for initiating resmetirom or to assess treatment response, because it was not developed for this context of use. Thus, FIB-4 should not be used to exclude patients who may benefit from treatment, in isolation. Instead, we advocate for its use in screening high-risk patients, such as those with cardiometabolic risk factors in primary care and endocrinology clinics to rule out advanced fibrosis as outlined in several clinical guideline management algorithms.[8,18]

Although the target treatment population for resmetirom was anchored to a histologic diagnosis in the pivotal clinical trials, it is impractical for liver biopsy to be performed in clinical practice. In the absence of a liver biopsy demonstrating at-risk MASH, NITs are necessary to identify the targeted treatment population. To enable the noninvasive identification of patients with different disease stages and assess response to treatment, NITs have been embedded into clinical trials, alongside liver biopsy. Acknowledging the impracticality of liver biopsy on a large scale, the FDA has left the noninvasive identification of eligible patients up to the clinician. The FDA label language indicates that treatment should be limited to patients with liver disease consistent with moderate to advanced fibrosis (consistent with stages F2 to F3 fibrosis), creating an important need for providers to use an evaluation cascade that will identify moderate to advanced fibrosis (F2 to F3) with consistency and reasonable certainty. Figure 1 summarizes proposed patient selection criteria for treatment with resmetirom. Herein we provide evidence-based best practices in identifying the target treatment population noninvasively with regard to which parameters, singly or in combination, indicate liver disease consistent with moderate to advanced fibrosis (F2 to F3) without cirrhosis.

Availability of NITs can vary across practice settings. Ideally, more than 1 NIT should be used to identify patients who are likely to have stage 2 or 3 fibrosis. For instance, in the case of ELF, all patients who entered the MAESTRO-NASH where preselected based on VCTE cutoff of 8.5 kPa and higher and thus the cohort was already enriched with advanced fibrosis. Data derived from less enriched cohorts suggest a cutoff of 9.8 may result in a lower rate of misclassification.[19,20] To reduce misclassification of patients as having clinically significant fibrosis, we recommend that providers use a cutoff of 9.8 when ELF is used in isolation (eg, where liver stiffness assessment is not available). In the setting where ELF is between 9.2 and 9.7 we recommend an additional NIT to confirm the likelihood of stage 2–3 fibrosis (Table 1).

Since the initiation of the MAESTRO-NASH trial,[1] new composite scores have been developed to assess at-risk MASH. Many simple or combined NITs, including VCTE (both VCTE [eg, FibroScan] or visual transient elastography [eg, Hepatus]) are approved by FDA for the assessment of liver stiffness: FibroScan–aspartate aminotransferase, magnetic resonance imaging (MRI) aspartate aminotransferase, and MRE + FIB-4 have been adopted by society guidelines.[8,21–24] Other serum biomarkers to assess at-risk MASH, such as NIS-2+ or metabolomics-advanced steatohepatitis fibrosis, are also evolving and may be considered.[25,26] Using the

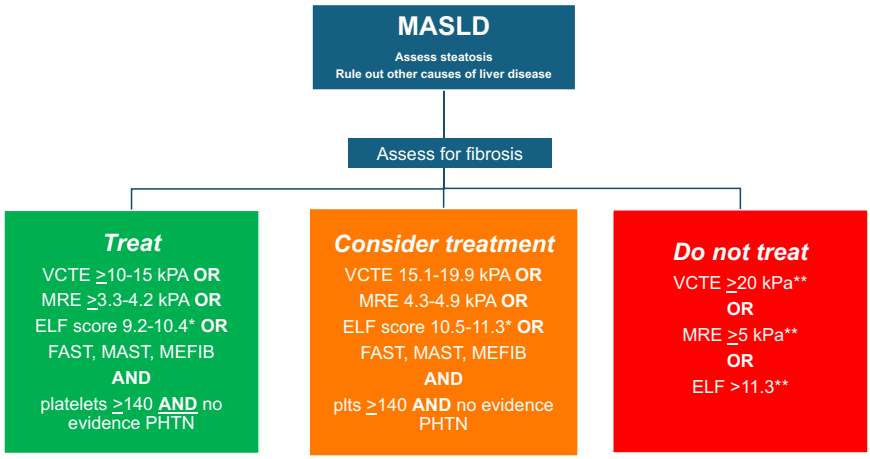

Figure 1. Proposed algorithm for patient selection using noninvasive tests. In patients with MASLD (steatosis confirmed on imaging or suspected by the presence of cardiometabolic risk factors and exclusion of other causes of liver disease), fibrosis burden should be approximated using NITs, with the goal of targeting those with clinically significant fibrosis (F2 or F3) and excluding those likely to have cirrhosis or PHTN. PeTH measurement should be considered to identify those who may have MetALD or alcoholic liver disease. Although treatment with resmetirom may be effective in the setting of moderate or heavy alcohol use, this requires further study. Thus, it is suggested that those with a PeTH >200 not be treated with resmetirom. If liver biopsy is available and demonstrates stage 2 or 3 fibrosis, NIT-based parameters can be overridden, provided there is no clinical or imaging evidence of PHTN (see text for specifics). FAST, FibroScan–aspartate aminotransferase; MAST, magnetic resonance imaging–aspartate aminotransferase; MEFIB, magnetic resonance elastography + Fibrosis-4; PeTh, phosphatidylethanol; PHTN, portal hypertension. *To reduce false positives, we propose that 2 concordant blood-based or liver stiffness above threshold values for VCTE or MRE that suggest the presence of significant/advanced fibrosis and not cirrhosis. In scenarios where only ELF is available in isolation, either a liver biopsy or a cutoff of 9.8 and higher is warranted. ** If biopsy is performed and liver histology demonstrates stage 2 or 3 disease, treatment is appropriate, as long as there is no clinical or imaging evidence of portal hypertension (eg, ascites apparent on imaging, gastroesophageal varices, history of hepatic encephalopathy).

MAESTRO-NASH baseline data and their quartile ranges, we suggest parameters to identify patients with moderate to advanced fibrosis without cirrhosis.

After complete assessment of baseline liver disease and confirmation of appropriateness for resmetirom treatment, patients should be dosed according to their weight, then monitored for safety and disease progression through regular liver chemistry tests, and yearly LSM.

Patients Who Should Not be Treated with Resmetirom

Patients with Confirmed or Suspected Cirrhosis

Because it is not possible for NITs to precisely determine disease stage, we suggest erring on the side of not treating patients on the earlier side of the spectrum and avoiding patients who are likely to have established cirrhosis, because the benefit of resmetirom in this population is still being assessed in a phase 3 cirrhosis trial and this patient population may require different dosing and assessment (Figure 1). The distinction between F3 and early F4 (cirrhosis) is challenging, thus it is not uncommon that such patients are misclassified. This was likely the case for some patients treated in the MAESTRO-NASH trial. Although resmetirom is likely safe in such patients, the drug should not be used in patients diagnosed with or suspected to have cirrhosis until full efficacy and safety data in patients with cirrhosis are published. With respect to the use of ELF in this context, used in isolation, it has a low positive predictive value. Recent data from the NIMBLE consortium showed that an ELF cutoff of approximately 10.3 had an area under the curve of 0.855 for detecting cirrhosis, with a sensitivity of 82.1% and specificity of 73.3%.[27] This cutoff also aligns with the baseline ELF value in patients with cirrhosis in the ongoing MAESTRO-Outcome study. The 10.4 value is also consistent with that chosen by the National Institute for Clinical Excellence as a threshold for "advanced" fibrosis (https://www.nice.org.uk/guidance/ng49/chapter/Putting-this-guideline-into-practice). Therefore, in those with ELF 10.4–11.3, an additional NIT (eg, FIB-4, elastography) should be consistent with F2 or F3 disease and not cirrhosis.

The MAESTRO OUTCOMES trial (NCT05500222), which is near full enrollment, will provide full efficacy and safety data in patients with compensated cirrhosis, which will guide dosing and future treatment decisions in this population.[16] Therefore, we suggest excluding those with advanced cirrhosis based on:

1. History of fibrosis stage 4 on liver biopsy.
2. Imaging with signs of portal hypertension, ascites, portosystemic venous collaterals, or varices, irrespective of liver biopsy.
3. History of clinical manifestations of hepatic decompensation (ie, ascites, gastro or esophageal varices, or hepatic encephalopathy), irrespective of liver biopsy.

4. Clinical or laboratory data suggesting portal hypertension or synthetic dysfunction, such as:
   a) VCTE stiffness >20 kPa[24] or MRE >5 kPa.
   b) Platelets <140,000/μL (which was an exclusion criteria in the trial) without alternative explanation. In the setting of isolated thrombocytopenia, consider corroborating evidence with NITs or biopsy if cirrhosis is of low suspicion.
   c) ELF >11.3 (those at increased risk for clinical outcomes).
   d) Hepatic nodularity on imaging not otherwise explained (eg, nodular regenerative hyperplasia).
   e) Elevated bilirubin, unless predominately indirect in range consistent with Gilbert syndrome or other concern for hepatic synthetic dysfunction (eg, elevated international normalized ratio or low albumin).

Patients with Early Stage Disease

Patients with early stage MASLD (no or early fibrosis [eg, stage 0 or 1]) should not be considered for resmetirom treatment because they are at very low risk for adverse liver-related outcomes. Such patients should be managed with lifestyle intervention and optimization of cardiometabolic disease as outlined in the AASLD practice guidance.[8]

Assessment of Treatment Response

Change in Noninvasive Tests Suggestive of Histologic Response

Substantial evidence has demonstrated an association between improvement in NITs, most notably liver enzymes and MRI–proton density fat fraction (PDFF), and improvement in liver histology and liver clinical outcomes.[13,14,28] Although the evidence linking thresholds of dynamic change in NITs to histologic response continues to evolve, practitioners need to make a clinical assessment using the tools at their disposal (Figure 1). With this caveat in mind, we suggest parameters that have been associated with histologic response in the resmetirom program and other clinical trials. In the instance of MASH, alanine aminotransferase (ALT) improvement by 17 U/L, has correlated with improved liver histology in other studies.[1,29,30] However, although improvement in ALT by 17 units correlated with histologic response in previous studies, in the MAESTRO-NASH study many patients had histologic improvement without ALT improvement. Thus, the lack of aminotransferase response should be interpreted cautiously, and other NITs (including imaging) should be assessed. Liver biopsy can be considered where data are discrepant or definitive assessment of response is desired.

Several studies suggest that reductions in VCTE stiffness by 20%–30% may correlate with histologic response.[31–33] To increase confidence that a change in VCTE is clinically meaningful, we recommend that changes in excess of 30% be considered meaningful (given coefficient of variation is approximately 30%), particularly in the case of worsening, because this has been shown to correlate with adverse outcomes.[12] Additionally, a decrease in ALT by 17 units (or 20% decline) could be considered a reasonable predictor of histologic response.[30,32] Changes in CAP score in isolation are insufficient to determine treatment response until further data are available. However, in combination with improvement in liver enzymes or liver stiffness, improved CAP score would support improvement in MASH.

However, a failure to exceed the proposed threshold response, may not be indicative of a treatment failure. Despite not exceeding the response thresholds proposed herein, many patients in the MAESTRO-NASH trial did demonstrate histologic improvement at 52 weeks. Therefore, the predictivity of the proposed NITs in isolation, should be interpreted with caution until further analysis from the MAESTRO-NASH trial is available.

Scores derived from liver enzymes and other parameters (eg, FibroScan–aspartate aminotransferase or MRI–aspartate aminotransferase) have also decreased in association with histologic response (unpublished data from MAESTRO-NASH). In the context of disease natural history, changes in MRE or VCTE liver stiffness and changes in Agile 3+, Agile 4, MRI–aspartate aminotransferase, and MRE + FIB-4 scores have also correlated with liver-related outcomes[12–14]; however, prospective validation of a direct correlation between favorable improvement in these biomarkers in the context of a pharmacologic intervention is needed. LSM improvements reflecting clinically meaningful change typically require 1 or more years and therefore, more frequent monitoring may be less helpful and cause confusion.

In the MAESTRO-NASH trial, 1 of the strongest predictors of histologic response (for both end points) was a ≥30% reduction in MRI-PDFF.[1] Specifically, patients on resmetirom who had a ≥30% relative reduction in MRI-PDFF, had a 30%–37% margin over placebo for NASH resolution, compared with a margin of only 4%–5% for patients with <30% relative reduction in MRI-PDFF. Similarly, patients on resmetirom who had a ≥30% relative reduction in MRI-PDFF, had a 17%–18% margin over placebo for fibrosis improvement (without worsening of NASH), compared with a margin of only 1%–1.5% for patients with <30% relative reduction in MRI-PDFF (See Supplementary Tables S10 and S12 of Harrison et al).[1] MRI-PDFF response of greater than or equal to versus less than a 30% drop in liver fat content differentiated histologic responders from nonresponders

at 16 weeks; however, in the absence of individual patient data, we hesitate to recommend treatment discontinuation based on this early assessment. Instead, assessment at 52 weeks should be used to assess treatment response on review of the totality of noninvasive assessment.

Long-term real-world data on patients treated with resmetirom should be gathered to further inform expected treatment duration. Nevertheless, treatment by resmetirom is expected to be long-term, similarly to treatment of concomitant diseases, such as type 2 diabetes, dyslipidemia, and hypertension.

Prevention of disease progression (ie, stability, as defined by stable readings [not worsening] in VCTE, liver enzymes, or MRI-PDFF) is clinically relevant but additional data are needed to make firm recommendations on the benefits of continuing treatment with resmetirom and adding on agents with potential benefit, versus switching to a different therapeutic, as available. The impact of maintaining disease stability will be more clearly informed by the 54-month assessment of the MAESTRO-NASH study, which will provide data on the prevention of progression to cirrhosis.

Parameters Suggestive of Treatment Failure

Those with worsening values on VCTE (>30%) suggest the possibility of disease progression and has been linked to worse outcomes.[12] Other data suggest that an increase of 5 kPa accompanied by a 20% increase in LSM measured by transient elastography, was associated with a poorer prognosis.[33] If there is no improvement in ALT, ≥30% reduction in PDFF can still be predictive of response. Similarly, VCTE alone may be inadequate to assess treatment response. Based on MAESTRO-NASH, histologic improvements may occur without corresponding changes in VCTE or liver enzymes, emphasizing the importance of considering MRI-PDFF or liver biopsy before labeling patients as unresponsive to treatment. Because of high variability in some NITs, we suggest that worsening in at least 2 NITs be considered clinically meaningful and indicative of treatment failure. Those with worsening values on VCTE (>30%), or liver enzymes (>20%), and/or MRI-PDFF (<30% relative to baseline improvement) can be considered reasonable candidates to pursue other strategies (eg, switching to another medication if FDA approved, keeping them on the drug while enrolling in clinical trials as allowed, or repeat liver biopsy if it was done at baseline) after completion of 12 months of therapy.

Until we have more robust data regarding NITs as reliable surrogates for histologic improvement, we recommend full efficacy assessment at 12 months of therapy, not before. Therefore, we suggest breaking the assessment of response to resmetirom into 3 periods:

1. *Initial assessment for safety and tolerability (Week 12).* Although there was no significant concern over hepatotoxicity in the MAESTRO-NASH trial, it is good practice to exclude the presence of a hepatotoxicity signal and to confirm the absence of concomitant liver disease with the initiation of any new drug.[34] At this early time point, assessment of efficacy is not appropriate. Given that changes in ALT, especially at the 12-week time point, do not accurately reflect treatment response, medical providers are advised to reserve judgment on efficacy to 12 months (Figure 2).
2. *Assessment at 6 months: disease monitoring* (Figure 2). Aminotransferases should be considered at 6 months for disease monitoring and VCTE or PDFF can be considered and may suggest early response. Importantly, the absence of response at 6 months may be inadequate to fully assess treatment response. Discontinue treatment if drug not tolerated (eg, debilitating gastrointestinal symptoms).
3. *Assessment at 12 months and annually: efficacy monitoring* (Figure 2).

Continue treatment if:

- Aminotransferases improved (compared with baseline or normalization).
- Aminotransferases are stable but other indication of disease improvement is present (eg, improvement in MRI-PDFF).
- In those who had MRI-PDFF at baseline, a reduction in MRI-PDFF of ≥30% suggests a likely histologic response.
- LSM should be part of regular patient monitoring every 12 months either by transient elastography or MRE; the use of a consistent method of LSM after initiating treatment is preferred (Figure 2).

Discontinue treatment if:

- No response in MRI-PDFF if obtained at baseline.
- >30% increase in liver stiffness or >2 NITs[17,27] worsen, as discussed previously and in Figure 2.
- Drug not tolerated.

Safety Considerations

Resmetirom has demonstrated a favorable safety and tolerability profile, based on the combined safety phase 3 population (2019 patients from 2 phase 3 trials, MAESTRO-NASH and MAESTRO-NAFLD-1). The package insert of resmetirom describes the most common adverse reactions reported in more than 5% of patients in the main registration trial, MAESTRO-NASH, using exposure-adjusted incidence rates. These rates are reported per 100 person-years. The most common adverse

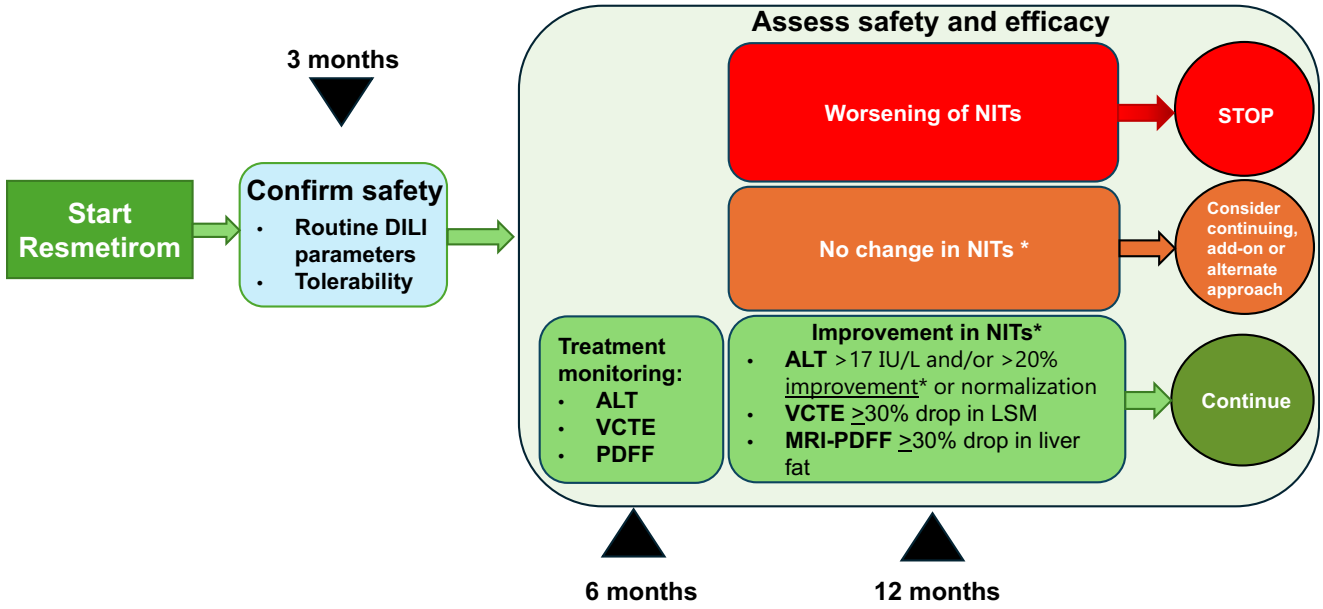

Figure 2. Assessment of safety and treatment response on resmetirom. Changes in NITs at 3 months were not reliably predictive of treatment response in the MAESTRO-NASH trial, thus the 3-month assessment should be reserved to confirm the absence of DILI. Assessment of response in patients with resmetirom should ideally not be made until the 12-month time point. Although an improvement in PDFF was most predictive of response, this may not be routinely performed and other NIT benchmarks to consider are provided. DILI, drug-induced liver injury; PDFF, proton density fat fraction. *ALT improvement should be accompanied by improvement in imaging (≥30 reduction in MRI-PDFF). If no improvement in ALT, ≥30% reduction in PDFF can still be predictive of response. VCTE alone may be inadequate to assess treatment response. Based on MAESTRO NASH, histologic improvements may occur without corresponding changes in VCTE or liver enzymes, emphasizing the importance of considering MRI-PDFF or liver biopsy before labeling patients as unresponsive to treatment.

reactions induced by resmetirom were mild to moderate gastrointestinal disorders, mainly nausea and diarrhea, followed by constipation, abdominal pain, and vomiting. These gastrointestinal disorders were dose-dependent, with the highest event rates reported in those receiving the highest dose of drug (ie, 100 mg/day). The median time to diarrhea onset was 17 and 6 days in the resmetirom 80-mg and 100-mg groups, respectively. The median duration of diarrhea was 20 days in both groups. Similarly, nausea generally occurred earlier, with a median time to onset of 5 days, at the high dose (100 mg), compared with the 80-mg group with a median time to onset of 28 days. The mean duration of nausea was 26 and 28 days in the resmetirom 80-mg and 100-mg groups, respectively. Diarrhea and nausea led to treatment discontinuation in 8 per 100 person-years in the high-dose group. Education of patients on potential gastrointestinal disorders is recommended to avoid unnecessary treatment discontinuations and increase the treatment persistence rates in real-world settings.

During clinical development of resmetirom, early increases in liver enzymes were observed in the first 4 weeks after initiating treatment, mainly in patients treated with statins at baseline. The mean ALT and aspartate aminotransferase increases was less than 1.5x baseline. Those increases rapidly returned to normal, within approximately 8 weeks after initiating treatment, and in the absence of treatment discontinuation. This pattern seems similar to those drug candidates currently in development where liver enzyme increases occur within the first 4–8 weeks after treatment initiation and are typically associated with substantial decreases in liver fat content.[34,35] In the package insert of resmetirom, an isolated case of potential hepatotoxicity has been described; 1 patient had liver enzymes elevation after initiating treatment with resmetirom, which resolved after treatment interruption.

Considerations for Stopping Resmetirom

We recommend checking liver enzymes 12 weeks after treatment initiation to assess for hepatotoxicity. Indeed, as described previously, the efficacy profile of the drug is consistent with possible early and mild transient increase in liver enzymes. As such, decisions to discontinue treatment should not be made before Week 12 because the interpretation of the data may be challenging. However, education of the patient on potential hepatotoxicity is of paramount importance (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, and/or rash), to ensure proper follow-up if needed. In the case of persistent and significant elevation of liver enzymes, at any time during the follow-up, treatment discontinuation should be carefully considered (Table 1).

Other Considerations

Resmetirom is a CYP2C8, OATP1B1, and OATPB1B3 substrate and as such, the concomitant use of resmetirom with strong CYP2C8 inhibitors (gemfibrozil) or OATP1B1 and OATPB1B3 substrate (eg, cyclosporine) is not recommended. The use of resmetirom with moderate CYP2C8 inhibitors (eg, clopidogrel) can be considered after dosage reduction of resmetirom and should trigger closer safety monitoring. Resmetirom increased plasma concentrations of some statins in late-phase clinical trials. Theoretically, this may increase the risk of adverse events related to statins, although none was observed thus far. For this reason, dosing of rosuvastatin and simvastatin should be limited to 20 mg/day and pravastatin and atorvastatin should be limited to 40 mg/day. All of these maximum recommended doses are at or above maximum standard dosing of these statins and consistent with the study population of MAESTRO-NASH.

The FDA has recommended a dosage adjustment of certain statins if used concomitantly with resmetirom. Within the phase 3 safety data supporting the approval of resmetirom (>2000 patients), approximately half of the patients were concomitantly treated with statins at baseline. This subpopulation had a similar efficacy/safety profile when compared with those patients without concomitant treatment with statins. The authors do not foresee any concern on statin dosage reduction as per the drug package insert, considering resmetirom has demonstrated significant effect on low-density lipoprotein reduction. Indeed, the percent change in low-density lipoprotein–cholesterol in patients with elevated baseline levels was -14% and -20% in the resmetirom 80-mg and 100-mg groups, respectively, versus 0% in the placebo group, after 52 weeks of treatment. As a consequence, there is no expected negative impact of statin dosage reduction in patients treated with resmetirom. Care providers should continue to adhere to low-density lipoprotein targets in patients at high risk of cardiovascular events and adjust statin dosage, or use other agents as appropriate.

Endocrinologic Considerations

Some concerns have been raised about the potential negative feedback regulation of the central hypothalamic-pituitary-thyroid axis together with its potential long-term impact on patient health because treatment with resmetirom for 52 weeks reduced serum-free T4 levels by approximately 16%–19%. In both phase 3 trials, no increase in endocrine adverse events was reported and there were no abnormalities in thyroid-stimulating hormone or T3/free T3, which remained within normal physiological limits. With resmetirom treatment, the upregulation of T4 to T3 conversion by type 1 deiodinase (DIO1) occurs exclusively within the liver, through the thyroid hormone receptor-β. There is no evidence of potential central regulation of the hypothalamic-pituitary-thyroid axis. Indeed, in case of central mediation of thyroid hormone by resmetirom, the increase in free T3 would result in a decrease in free T4; this decrease would be higher in patients treated without thyroid pathology versus those without thyroid tissue (thus unable to be regulated by central mediation) and treated with full hormone replacement. However, there was no difference in free T4 average decrease between these 2 populations, supporting the absence of central hypothalamic-pituitary-thyroid axis regulation by resmetirom.[1] It has also been shown, in animal models, that increases in DIO1 results in an increased clearance of T3, which is consistent with the absence of changes in T3/free T3 or thyroid-stimulating hormone in patients treated with resmetirom.[36] Resmetirom does not interfere with thyroid hormone replacement therapy and can be coadministered, although future studies will assess the impact on thyroid monitoring or bone health, if any.

Sex hormone–binding globulin levels were elevated in patients treated with resmetirom as a reflection of target engagement. This resulted in slight changes in sex hormone levels. Some concerns have been raised on the potential long-term consequences, although free testosterone levels remained unchanged and there was no change in bone mineral density. To date, the accumulated safety data do not suggest a cause for concern.

Concomitant Use of GLP-1 or GLP-1/GIP Dual Agonists

The use of treatment with GLP-1 receptor agonist or dual GIP and GLP-1 receptor agonists are rapidly increasing in the United States for the treatment of obesity and type 2 diabetes and thus, are frequently used for the management of these comorbidities in patients with MASH.[37] For patients currently managed with these therapies, we recommend initiating resmetirom in case of residual active MASH with stage 2 or 3 fibrosis. Existing GLP-1 receptor agonist therapy, which was present at baseline in ~14% of patients in the MAESTRO-NASH, did not seem to affect tolerability or efficacy of resmetirom. Because of the lack of evidence supporting the efficacy and safety of initiation of GLP-1-based therapy and resmetirom concomitantly, this is not recommended. In "GLP-1 and resmetirom naive" patients with MASH and fibrosis consistent with F2 or F3 in particular, clinicians must balance risk and benefits of each therapy in the settings of a specific patient's profile, keeping in mind that only resmetirom, to date, has demonstrated effect on both MASH resolution and fibrosis regression in a large phase 3 registration trial. These recommendations are in line with the most recent European Association for the Study of Liver disease guidelines for the diagnosis and treatment of MASH.[38] Resmetirom is the only liver-directed therapy currently FDA-approved.

Summary

On March 14, 2024, the FDA approved resmetirom as pharmacotherapy for MASH. Patients approved for treatment with resmetirom include those who have developed stage 2 or stage 3 fibrosis and have "at-risk MASH." At this point, patients with cirrhosis and those with early (F0-1) fibrosis should not be treated with resmetirom. Liver biopsy or NITs can be used to identify patients who should be considered for resmetirom treatment, monitor safety, and to determine treatment efficacy. Emerging data, particularly regarding the noninvasive assessment of treatment response, are likely to further modify patient selection, safety signals, and efficacy algorithms.

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Conflicts of interest

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