

New and Emerging Therapies for Metabolic Dysfunction-Associated Steatotic Liver Disease/Metabolic Dysfunction-Associated Steatohepatitis (MASLD/MASH) in Adults

Sara Fletcher, PharmD, MPH, BCPS, Oregon State University Drug Use Research and Management Group

Introduction

The American Association for the Study of Liver Diseases (AASLD) introduced new nomenclature for fatty liver disease in June 2023. Steatotic liver disease is the new umbrella term describing hepatic steatosis, with subcategories that include metabolic dysfunction-associated steatotic liver disease (MASLD) and MASLD with increased alcohol intake (MetALD).¹ The terms MASLD and metabolic dysfunction-associated steatohepatitis (MASH) were introduced in place of nonalcoholic fatty liver disease (NAFLD) and its subcategory nonalcoholic steatohepatitis (NASH).¹⁻³ MASLD is defined by the presence of hepatic steatosis on imaging or biopsy and at least one cardiometabolic risk factor of: increased body mass index (BMI) or waist circumference; increased fasting glucose or hemoglobin A1C (HbA1C) or type 2 diabetes (T2D); hypertension; elevated plasma triglycerides; or decreased high-density lipoprotein (HDL).¹

MASH is a subcategory of MASLD which includes inflammation and hepatocyte injury (e.g., hepatocyte ballooning), with or without evidence of liver fibrosis.⁴ MASLD affects about 25% of people worldwide, and 12-14% of those with MASLD are estimated to have MASH.⁴ Complications can include cirrhosis, hepatic decompensation, and death.

Fibrosis Stage

Once diagnosed, MASH is described by stages of fibrosis (Table 1).

Table 1. Stages of MASH Fibrosis^{4,5}

Fibrosis Stages	Description
No Fibrosis (F0)	None
Stage 1, Mild (F1)	Perisinusoidal OR periportal fibrosis
• F1A	• Mild perisinusoidal fibrosis
• F1B	• Moderate perisinusoidal fibrosis
• F1C	• Only portal/periportal fibrosis
Stage 2 Moderate (F2)	Perisinusoidal AND portal/periportal fibrosis
Stage 3, Severe (F3)	Bridging fibrosis
Stage 4, Cirrhosis (F4)	Cirrhosis

Treatment

Historically no medications have been specifically indicated for MASH. Treatment focuses on cardiometabolic risk factor management including guideline-directed therapy for T2D, dyslipidemia, obesity, metabolic syndrome, prediabetes, hypertension, and cardiovascular disease.⁴

Pioglitazone and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended for people with T2D and biopsy-proven MASH and should be considered when there is increased risk of MASH based on presence of risk factors and likelihood of fibrosis using non-invasive tests (e.g., fibrosis-4 index [FIB-4]).^{4,6} However, pioglitazone has notable side effects, including weight gain and potential risk for worsening heart failure which may preclude use in general practice.^{4,6} In large phase III trials, pioglitazone did not improve liver histology or fibrosis in non-cirrhotic MASH, though multiple smaller studies with lower quality evidence have shown improvement in fibrosis.^{3,7} In people with T2D and MASLD, American Academy of Clinical Endocrinology (AACE) recommends providers consider pioglitazone, GLP-1 RAs, or sodium-glucose cotransporter-2 (SGLT2) inhibitors for cardiometabolic benefit, though there is no evidence of benefit for liver related outcomes with SGLT2 inhibitors.⁴ Some guidelines also suggest vitamin E for people with MASH but without comorbid T2D or advanced fibrosis.^{4,8} Not all organizations recommend vitamin E because of potential long-term side effects (i.e., cardiovascular disease, prostate cancer) and large phase 3 trials did not show robust improvement in histologic outcomes compared to placebo.^{3,7}

Weight Management

Lifestyle interventions (e.g., diet and exercise) are recommended for all adults with MASLD.⁴ In adults with MASLD and overweight, weight loss of at least 5% reduces liver fat and has cardiometabolic benefits, 7-10% reduces liver inflammation, and 10% or more improves fibrosis and may reverse steatohepatitis.^{3,4}

For people with MASLD and BMI of at least 27 kg/m², the AACE recommends the addition of semaglutide 2.4 mg/week or liraglutide 3 mg/day when weight management goals are not effectively achieved by lifestyle interventions alone.⁴ Hepatic histologic benefit could be expected if substantial weight loss is induced by GLP-1 RAs. There is a similar a safety profile for use in patients with MASH (including compensated cirrhosis) and they are recommended for use with indications of T2D and obesity due to cardiometabolic benefits.³ Bariatric surgery is also an option to treat MASLD and improve cardiometabolic health in some patients.^{3,4}

Medicaid compendia (i.e., Micromedex) support use of semaglutide and liraglutide for MASH in adults with overweight or obesity based on results of phase 2 studies.^{9,10} A phase 2 trial supporting tirzepatide in MASH is also published.¹¹ Semaglutide in patients with fibrosis stage 4 did not improve fibrosis or resolution of MASH.¹² A phase 2 study of daily dosed injectable semaglutide (0.1 mg, 0.2 mg, 0.4 mg) in stage 1, 2, or 3 showed improvement for MASH resolution and fibrosis improvement at week 72 compared to placebo (**Table 2**). The phase 2 SYNERGY-NASH study of weekly dosed tirzepatide (5 mg, 10 mg, 15 mg) in stage 2 or 3 fibrosis also showed resolution of MASH and improvement of fibrosis (**Table 2**) at week 52.¹¹ Though not a primary endpoint, a 10.7-15.6% weight loss was seen in tirzepatide treated patients and 5-13% in semaglutide treated patients.^{11,13} Studies of liraglutide included fewer participants and evaluated slightly different outcomes. Details of these studies are available at:

https://www.orpd.org/durm/meetings/meetingdocs/2024_08_01/archives/2024_08_01_Rezdifra_NDE.pdf.

Table 2. Selected GLP-1 RA phase 2 studies*^{11,13}

	MASH Resolution	Fibrosis Improvement
Semaglutide 0.1 mg	40% OR 3.36 (95% CI 1.29-8.86)	49% OR 1.96 (95% CI 0.86-4.51)
Semaglutide 0.2 mg	36% OR 2.71 (95% CI 1.06-7.56)	32% OR 1.00 (95% CI 0.43-2.32)
Semaglutide 0.4 mg	59% OR 6.87 (95% CI 2.60-17.63)	43% OR 1.42 (95% CI 0.62-3.28)
Placebo	17%	33%
Tirzepatide 5 mg		
	44% Difference 34% (95% CI 17-50)	55% Difference 25% (95% CI 5-46)
Tirzepatide 10 mg		
	56% Difference 46% (95% CI 29-62)	51% Difference 22% (95% CI 1-42)
Tirzepatide 15 mg		
	62% Difference 53% (95% CI 36-69)	51% Difference 21% (95% CI 1-42)
Placebo	10%	30%
*Results from unique studies; not for direct comparison CI=confidence interval; MASH=metabolic dysfunction-associated steatohepatitis; OR=odds ratio		

Resmetirom

Resmetirom, a partial agonist of the thyroid hormone receptor-beta (THR-β) was approved by the FDA in March 2024 through the FDA accelerated approval pathway. It is indicated, in conjunction with diet and exercise, for the treatment of adults with MASH who have moderate to advanced liver fibrosis (F2 to F3).¹⁴ Per FDA guidance, fibrosis staging and NAFLD activity score (NAS) are used in clinical trials as critical inclusion criteria and surrogate outcomes for testing.¹⁵ Improved mortality has not yet been demonstrated from histologic changes.³ The NAS is an unweighted composite 0 to 8 point score determined by the summation of three components: steatosis grade, lobular inflammation, and ballooning scores.⁴ Continued approval is contingent upon verification and description of clinical benefit (e.g., death from any cause, liver transplantation, hepatic decompensation events) in confirmatory trials.¹⁴ Evidence for efficacy and safety of resmetirom is from an ongoing phase 3 trial which enrolled adults who had at least 3 of 5 metabolic risk factors, biopsy confirmed MASH, and a NAS total score of 4 or more with presence of histological steatosis, lobular inflammation, and ballooning.¹⁶ The intention-to-treat primary population (N=966) consisted of all randomized patients with F1B, F2, and F3 fibrosis stage, and the primary biopsy analysis population (N=955) included those with paired biopsies.¹⁶ Patients were White (89.3%), with mean BMI of more than 35 kg/m², T2D (67% with baseline HbA1C ~6.6%), hypertension (78.1%), and dyslipidemia (71.3%), and no history of atherosclerotic cardiovascular disease (ASCVD) (5.9%).¹⁶ For those with T2D, 21% were on a GLP-1 RA, 20% on an SGLT2 inhibitor, and 18.2% on insulin. Those with an HbA1C of more than 9% were excluded.¹⁶ For those with dyslipidemia, 68.7% were taking a statin.¹⁶

There were two primary endpoints: MASH resolution and fibrosis improvement. MASH resolution at week 52 was defined as achievement of hepatocellular ballooning score of 0, lobular inflammation score of 0 to 1, and reduction of NAS by 2 or more points with no worsening of fibrosis.¹⁶ The second primary endpoint was defined as improvement in fibrosis by at least one stage without worsening of NAS.¹⁶ Results compared to placebo are in **Table 3**. There was no effect on body weight or heart rate.¹⁶ Most adverse events were mild to moderate, with diarrhea (27-33.4%) lasting a median of 15-20 days being most common. Discontinuation due to adverse events were more frequent in the resmetirom 100 mg group (6.8%) than resmetirom 80mg (1.8%) or placebo (2.2%).¹⁶ Dosing in the study was randomly assigned; dosing by FDA label is weight-based with the 100 mg dose reserved for people weighing 100 kg or more. Drug interactions (e.g., certain statins) may require dose reduction. Long-term safety remains unknown.

Table 3. MAESTRO-NASH Primary Endpoints Results OHP Policy

	MASH Resolution	Fibrosis Improvement
Resmetirom 80 mg	25.9% 95% CI 11.0 to 21.8% p<0.001	24.2% 95% CI 4.8 to 15.7% p<0.001
Resmetirom 100 mg	29.9% 95% CI 15.3 to 26.2% p<0.001	25.9% 95% CI 6.4 to 17.2% p<0.001
Placebo	9.7%	14.2%

CI=confidence interval; MASH=metabolic-dysfunction steatohepatitis

Use of resmetirom is available with prior authorization for eligible patients with Oregon Health Plan (OHP) open card benefits. Use of GLP-1 RAs with compendia support for MASH can be covered with prior authorization for Medicaid members with both overweight/obesity and MASH. OHP will continue to cover GLP-1 RAs for people with T2D who are taking or have contraindications to metformin.

Conclusion

MASH is an important cause of liver disease which is increasing in prevalence as metabolic risk factors increase. Risk factor management is a primary component of care for patients with MASH. A novel medication, resmetirom, has received accelerated approval for treatment of stage F2 or F3 MASH in conjunction with lifestyle changes. It was tested in patients with multiple risk factors and HbA1C less than 9% and demonstrated histologic improvements in MASH and fibrosis in some patients compared to placebo. Efficacy for other clinical outcomes is unknown. Additionally, evidence supporting the use of certain GLP-1 RAs is increasing. It is unclear if GLP-1 RA induced weight loss is the primary driver for improvements seen in MASH and fibrosis in phase 2 studies. OHP will cover resmetirom, liraglutide, and semaglutide for Oregon fee-for-service members who have MASH and who meet prior authorization criteria.

Key Points

- Management of modifiable risk factors, including weight loss, is important for treatment of MASH.
- Resmetirom is a new medication approved for MASH based on histologic improvement in a phase 3 study.
- Liraglutide, semaglutide, and tirzepatide have phase 2 evidence of histologic improvement in MASH.
- Prior Authorization criteria for resmetirom and certain GLP-1 RAs are available at: <https://www.orpd.org/drugs/>

Peer Reviewed By: Manida Wungjiranirun MD, Assistant Professor of Medicine, Director of the Multi-Disciplinary MASLD Clinic, Division of Gastroenterology and Hepatology at OHSU and Dekey Lhewa MD, Assistant Professor of Medicine, Division of Gastroenterology and Hepatology at OHSU

References:

- Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol.* Dec 2023;79(6):1542-1556. doi:10.1016/j.jhep.2023.06.003
- Veterans Affairs pharmacy benefit management services and national formulary committee. Resmetirom (REZDIFFRA) in metabolic dysfunction-associated steatohepatitis (MASH) criteria for use. April 2024. Available at: www.va.gov/formularyadvisor/DOC_PDF/CFU_Resmetirom_REZDIFFRA_in_Metabolic_Dysfunction-associated_Steatohepatitis_Criteria_Apr_2024.pdf.
- EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): Executive Summary. *Diabetologia.* Jun 13 2024;13:13. doi:<https://dx.doi.org/10.1007/s00125-024-06196-3>
- Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract.* May 2022;28(5):528-562. doi:10.1016/j.eprac.2022.03.010
- Duarte-Rojo A, Altamirano JT, Feld JJ. Noninvasive markers of fibrosis: key concepts for improving accuracy in daily clinical practice. *Ann Hepatol.* 2012;11(4):426-439. doi:10.1016/s1665-2681(19)31456-5
- Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology.* May 1 2023;77(5):1797-1835. doi:10.1097/HEP.000000000000323
- Non-alcoholic fatty liver disease assessment and management. (2016) NICE guideline NG49. Available at: <https://www.nice.org.uk/guidance/ng49>.
- Long MT, Nouredin M, Lim JK. AGA Clinical Practice Update: Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Lean Individuals: Expert Review. *Gastroenterology.* Sep 2022;163(3):764-774 e1. doi:10.1053/j.gastro.2022.06.023
- Liraglutide. In: Micromedex [database on the Internet]. Greenwood Village (CO): IBM Corporation; Last modified June 26, 2024. Available from: www.micromedexsolutions.com. Subscription required to view.
- Semaglutide. In: Micromedex [database on the Internet]. Greenwood Village (CO): IBM Corporation; Last modified June 26, 2024. Available from: www.micromedexsolutions.com. Subscription required to view.
- Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis. *N Engl J Med.* Jun 8 2024;doi:10.1056/NEJMoa2401943
- Loomba R, Abdelmalek MF, Armstrong MJ, et al. Semaglutide 2.4 mg once weekly in patients with non-alcoholic



steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol Hepatol*. Jun 2023;8(6):511-522.

doi:10.1016/S2468-1253(23)00068-7

13. Newsome PN, Buchholtz K, Cusi K, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med*. Mar 25 2021;384(12):1113-1124.

doi:10.1056/NEJMoa2028395

14. Rezdiffra (resmetirom) prescribing information. Madrigal Pharmaceuticals. West Conshohocken, PA. March 2024. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2024/217785s000lbl.pdf.

15. US Department for Health and Human Services. Noncirrhotic nonalcoholic steatohepatitis with liver fibrosis: developing drugs for treatment guidance for industry (draft guidance). December 2018. Available at:

<https://www.fda.gov/media/119044/download?attachment>.

16. Harrison SA, Bedossa P, Guy CD, et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. *N Engl J Med*. Feb 8 2024;390(6):497-509.

doi:10.1056/NEJMoa2309000