

New Therapies for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD/MASH): Clinical Outcomes and Implementation Challenges

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ABSTRACT

Introduction: metabolic dysfunction-associated fatty liver disease (MASLD) and its progressive inflammatory form, associated steatohepatitis (MASH), represent a growing challenge due to their high prevalence and potential progression to advanced fibrosis and cirrhosis. In recent years, the therapeutic approach has gone beyond lifestyle and dietary measures, driving the development of pharmacological alternatives aimed at modifying the natural history of the disease.

State of the art: recent research has focused on drugs that act on metabolic, inflammatory, and antifibrotic pathways involved in the pathophysiology of MASLD/MASH. Phase II and III clinical trials have shown promising results, notably glucagon-like peptide-1 (GLP-1) receptor agonists and selective thyroid hormone beta receptor agonists, which have shown improvement in the resolution of steatohepatitis and a decrease in the degree of liver fibrosis.

Discussion: despite the advances observed, therapeutic efficacy is not uniform among patients, suggesting pathophysiological heterogeneity and the need for personalized medicine strategies. Questions also remain regarding long-term safety, therapeutic adherence, and cost-benefit ratios in different healthcare settings, which are key aspects for their incorporation into routine clinical practice.

Conclusion: emerging drug therapies for MASLD and MASH represent a significant advance in the management of these conditions, offering significant clinical and histological benefits. However, optimizing their implementation requires further evidence on long-term safety, appropriate patient selection, and strategies to facilitate their effective integration into healthcare systems.

Keywords: MASLD, MASH, emerging therapies, liver fibrosis, FXR agonists, GLP-1.

Nuevas terapias para enfermedad hepática por depósito graso/metabólica (MASLD/MASH): resultados clínicos y retos en implementación

RESUMEN

Introducción: la enfermedad hepática por depósito graso asociada a disfunción metabólica (MASLD) y su forma inflamatoria progresiva, la esteatohepatitis asociada (MASH), representan un desafío creciente

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Received: 01/10/2026 | Accepted: 09/02/2026 | Published: 09/28/2026

DOI: <http://doi.org/10.51987/Rev.Hosp.Ital.B.Aires.v46i3.1314>

How to cite: Flores JJ, Aguilera EP. New Therapies for Metabolic Dysfunction-Associated Steatotic Liver Disease/Steatohepatitis (MASLD/MASH): Clinical Outcomes and Implementation Challenges. *Rev Hosp Ital B.Aires.* 2026;46(3):e0001314

por su alta prevalencia y su potencial evolución hacia fibrosis avanzada y cirrosis. En los últimos años, el abordaje terapéutico ha trascendido las medidas higiénico-dietéticas, impulsando el desarrollo de alternativas farmacológicas orientadas a modificar la historia natural de la enfermedad.

Estado del arte: la investigación reciente se ha centrado en fármacos que actúan sobre vías metabólicas, inflamatorias y antifibróticas implicadas en la fisiopatología de MASLD/MASH. Los ensayos clínicos de fases II y III han mostrado resultados prometedores, destacando los agonistas del receptor del péptido similar al glucagón tipo 1 (GLP-1) y los agonistas selectivos del receptor beta de hormona tiroidea, los cuales han evidenciado mejoría en la resolución de la esteatohepatitis y disminución del grado de fibrosis hepática.

Discusión: a pesar de los avances observados, la eficacia terapéutica no es uniforme entre los pacientes, lo que sugiere heterogeneidad fisiopatológica y necesidad de estrategias de medicina personalizada. Asimismo, persisten interrogantes con respecto a la seguridad a largo plazo, la adherencia terapéutica y la relación costo-beneficio en distintos contextos sanitarios, aspectos clave para su incorporación en la práctica clínica habitual.

Conclusión: las terapias farmacológicas emergentes para MASLD y MASH constituyen un avance relevante en el manejo de estas entidades, al ofrecer beneficios clínicos e histológicos significativos. Sin embargo, la optimización de su implementación requiere mayor evidencia sobre seguridad prolongada, selección adecuada de pacientes y estrategias que faciliten su integración efectiva en los sistemas de salud.

Palabras clave: MASLD, MASH, terapias emergentes, fibrosis hepática, agonistas FXR, GLP-1.

INTRODUCTION

MASLD is characterized by hepatic fat accumulation associated with metabolic conditions such as obesity, dyslipidemia, and insulin resistance. The disease's complex, multifactorial pathophysiology has made the search for effective therapies challenging. Current interventions include lifestyle modifications, metabolic control, and emerging targeted pharmacological therapies.¹

Treatment of metabolic dysfunction-associated steatotic liver disease/metabolic dysfunction-associated steatohepatitis (MASLD/MASH) is evolving rapidly, with new therapies targeting metabolic, inflammatory, and fibrogenic mechanisms. Lifestyle intervention remains the cornerstone of treatment; however, poor adherence and limited long-term effectiveness have driven the development of several pharmacological therapies supported by robust clinical evidence, as summarized in Table 1.^{2,3}

Laboratory medicine has promoted the integration of direct serum biomarkers that assess active extracellular matrix (ECM) turnover. These biomarkers quantitatively measure matrix synthesis and degradation by activated hepatic stellate cells.⁴

Direct panel (ELF score): The Enhanced Liver Fibrosis (ELF) score is an algorithm that combines hyaluronic acid (HA), the N-terminal propeptide of type III procollagen

(PIIINP), and tissue inhibitor of metalloproteinase-1 (TIMP-1). The ELF score provides a direct assessment of tissue remodeling independent of hepatocellular injury. Values <7.7 can rule out advanced liver fibrosis (ALF) with a high negative predictive value, whereas values ≥9.8 identify patients with MASLD at high risk of decompensation and vascular events.⁴

Metabolic Composite Algorithm (ADAPT score): Specifically designed to address the pathophysiology of MASLD, the ADAPT model combines age, the presence of type 2 diabetes (T2D), and platelet count with PRO-C3, a neoepitope marker of active type III collagen formation. By incorporating glycemic status and real-time fibrogenic activity, the ADAPT score achieves greater diagnostic accuracy [area under the receiver operating characteristic curve (AUROC) >0.86] for detecting advanced fibrosis in MASLD compared with conventional indirect tests.⁵

Regarding clinical outcomes, MASLD progresses to MASH in approximately 15–40% of patients, and fibrosis progresses more rapidly in MASH than in simple steatosis. Significant fibrosis (≥F2) is the main predictor of liver-related complications and mortality, while fibrosis regression is associated with better outcomes.^{1,6}

Implementation challenges include low rates of early diagnosis, particularly among high-risk populations such as individuals with type 2 diabetes, obesity, and cardiometabolic risk factors. Although

Table 1. Drugs Investigated for the Treatment of Metabolic Dysfunction–Associated Steatotic Liver Disease

Drug	Mechanism of Action	Pathophysiological Rationale
Resmetirom	Selective thyroid hormone receptor beta (THR- β) agonist	Stimulates hepatic β -oxidation and cholesterol catabolism, decreases de novo lipogenesis, counteracts “hepatic hypothyroidism,” and directly reduces steatosis, inflammation, and fibrosis
Obeticholic acid	Farnesoid X receptor (FXR) agonist	Reduces de novo lipogenesis, increases fatty acid oxidation, improves insulin sensitivity, and reduces hepatic inflammation and fibrosis
Tropifexor	FXR agonist	Acts through the same metabolic pathway as obeticholic acid, inhibiting lipid accumulation and attenuating the proinflammatory and profibrotic cascade in hepatic stellate cells
Pioglitazone	Peroxisome proliferator-activated receptor gamma (PPAR γ) agonist	Improves insulin sensitivity in adipose tissue and skeletal muscle, redistributes fat away from the liver, and reduces lipotoxicity and oxidative stress
Saroglitazar	PPAR α / γ agonist	PPAR α activation reduces triglycerides and enhances β -oxidation, while PPAR γ activation improves insulin sensitivity, simultaneously targeting dyslipidemia and steatosis
Elafibranor	PPAR α / δ agonist	PPAR α activation reduces lipids and inflammation, while PPAR δ activation improves glucose homeostasis and steatosis and attenuates hepatic stellate cell activation
Semaglutide	Glucagon-like peptide-1 (GLP-1) receptor agonist	Promotes significant weight loss, improves insulin secretion, delays gastric emptying, and reduces systemic lipotoxicity and inflammation
Liraglutide	GLP-1 receptor agonist	Similar to semaglutide, it improves glycemic control, reduces body weight, and decreases hepatic lipid accumulation through both indirect and direct mechanisms
Tirzepatide	GLP-1 and GIP receptor agonist	Enhances weight loss and glycemic control through synergistic receptor activity, markedly reducing liver fat content and inflammation
Pegbelfermin	Fibroblast growth factor 21 (FGF21) analog	Regulates lipid and glucose metabolism, increases adiponectin, improves insulin sensitivity, and reduces steatosis and fibrosis
Efruxifermin	FGF21 analog	Normalizes hepatic metabolism, decreases endoplasmic reticulum stress, reduces inflammation, and reverses hepatic fibrosis
Aldafermin	FGF19 analog	Suppresses bile acid synthesis through CYP7A1 (cytochrome P450 family 7 subfamily A member 1), decreases de novo lipogenesis, and inhibits inflammatory and fibrotic responses
Aramchol	Inhibitor of de novo lipid synthesis	Modulates fatty acid metabolism in hepatocytes, reducing triglyceride storage and associated inflammation
Cenicriviroc	CCR2 and CCR5 chemokine receptor antagonist	Blocks the recruitment of proinflammatory monocytes/macrophages to the liver, interrupting the inflammatory and profibrotic cascade
Selonsertib	Apoptosis signal-regulating kinase 1 (ASK1) inhibitor	Inhibits the p38/JNK signaling pathway activated by oxidative stress, thereby preventing hepatocyte apoptosis and associated fibrosis

GIP: glucose-dependent insulinotropic polypeptide.

screening with indices such as the Fibrosis-4 (FIB-4) index is recommended in these populations, it remains underused.^{2,7}

New therapies for metabolic dysfunction –associated steatotic liver disease/metabolic dysfunction– associated steatohepatitis (MASLD/MASH), including GLP-1 receptor agonists (semaglutide and tirzepatide) and the selective thyroid hormone receptor beta (THR- β) agonist resmetirom, which has been approved by the US Food and Drug Administration (FDA) for noncirrhotic MASH with F2-F3 fibrosis, differ from traditional approaches (lifestyle modification, management of metabolic comorbidities, and, in selected cases, vitamin E or pioglitazone) in several aspects of clinical efficacy.^{8,9}

For reducing steatosis and improving metabolic parameters, GLP-1 receptor agonists have shown greater efficacy than conventional interventions, particularly for weight loss and improved insulin resistance, both key factors in the pathophysiology of MASLD/MASH.¹⁰ Clinical trials have shown that semaglutide and tirzepatide achieve higher rates of steatohepatitis resolution and fibrosis regression than placebo and previously available pharmacological options, although they have not yet been specifically approved for MASH outside the United States.^{11,12}

However, the clinical efficacy of these new therapies should be interpreted in context. Although they have shown greater efficacy for histological and metabolic endpoints, their effects on hard clinical outcomes, such as progression to cirrhosis, major liver-related events, and mortality, are still being evaluated over the long term. Data on mortality and progression to cirrhosis are expected from the 54-month extensions of phase III trials (e.g., MAESTRO-NASH), with results anticipated in 2026-2027. Traditional approaches also remain essential, particularly in the early stages of disease and in patients with contraindications to newer therapies.^{13,14}

STATE OF THE ART

Emerging Therapies (Table 2)

1. FXR Agonists

Farnesoid X receptor (FXR) agonists, such as obeticholic acid and cilofexor, modulate bile acid homeostasis, thereby reducing hepatocellular stress and fibrosis in MASH.¹⁵ Although phase III trials have shown improvements in inflammation and fibrosis, their regulatory development has been limited by key adverse effects, primarily increases in low-density lipoprotein cholesterol (LDL-C) levels, which typically require concomitant statin therapy, and the development of dose-dependent pruritus.^{16,17}

2. GLP-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, have shown substantial effects on reducing liver fat and promoting weight loss, thereby indirectly improving insulin resistance and hepatic inflammation.¹⁸

In the phase III ESSENCE trial, semaglutide at a dose of 2.4 mg once weekly for 72 weeks achieved MASH resolution without worsening of fibrosis in 62.9% of patients, compared with 34.3% in the placebo group, and fibrosis improvement in 36.8% versus 22.4%, respectively. However, its effect on fibrosis regression is more modest, and efficacy has not been demonstrated in patients with cirrhosis.¹⁹

3. Antifibrotic Therapies

Agents targeting fibrotic mechanisms, such as pegbelfermin and integrin inhibitors, are being investigated. Preliminary findings indicate reductions in fibrosis markers and histological improvements. Antifibrotic therapies targeting fibrogenic pathways include FGF21 analogs, such as pegbelfermin and pegozafermin, as well as integrin inhibitors.²⁰

At higher doses, pegozafermin achieved fibrosis regression in up to 20% of patients and MASH resolution in 24% after six months of treatment. Integrin inhibitors remain in the early stages of investigation, with initial data suggesting reductions in markers of hepatic stellate cell activation but no robust results for histological endpoints.²¹

Implementation Challenges

Implementing new therapies for MASLD/MASH faces multiple clinical, regulatory, and logistical challenges. The pathophysiological heterogeneity of MASLD/MASH complicates the selection of optimal treatment for individual patients. The disease involves complex metabolic, inflammatory, and fibrogenic pathways, which may limit the efficacy of therapies targeting a single mechanism.^{22,23}

The clinical implementation of these therapies faces additional barriers:¹

- Access and cost: New medications are often expensive and have limited availability, potentially exacerbating health inequalities.
- Polypharmacy and comorbidities: Particularly in older adults, multiple comorbidities and the concomitant use of several medications increase the risk of drug interactions and adverse effects, requiring careful medication review and adjustment of therapeutic goals.
- Lack of data in special populations: Although recent clinical trials have included older adults, further evidence is needed in pediatric populations, patients with cirrhosis, and those with multiple comorbidities.
- Adherence and sustainability: The effectiveness of lifestyle interventions remains limited in real-world practice, and long-term adherence to pharmacological treatment remains challenging.

CONCLUSIONS

Evidence from phase II and III clinical trials indicates that multiple therapeutic classes, including incretin receptor agonists, nuclear receptor modulators (FXR,

Table 2. Pharmacological Therapies for MASLD/MASH – Integrated Table

Drug Class	Mechanism of Action	Liver Fibrosis	Hepatic Steatosis	Effect on Weight	Cardiorenal Effects	MASH resolution	Main Limitations
PPAR agonists (e.g., lanifibranor, pioglitazone)	Improve lipid metabolism and insulin sensitivity through PPAR activation	Moderate improvement	Moderate to significant reduction	Weight gain or neutral	Metabolic benefits; risk of heart failure with pioglitazone	Moderate	Weight gain, edema, and long-term safety concerns
GLP-1 receptor agonists (semaglutide, tirzepatide)	Increase insulin secretion, reduce appetite, and exert anti-inflammatory effects	Significant improvement in fibrosis markers and histology	Marked reduction in liver fat	Significant weight loss	Cardiovascular benefits and potential renal benefits	High rates in clinical trials	Cost, gastrointestinal adverse effects, and limited long-term data
SGLT2 inhibitors (sodium-glucose cotransporter 2 inhibitors; empagliflozin, dapagliflozin)	Block renal glucose reabsorption	Modest improvement	Mild reduction	Moderate weight loss	Well-established cardiorenal protection	Limited evidence	Limited histological evidence
FXR agonists (e.g., obeticholic acid)	Reduce hepatic lipogenesis and bile acid synthesis through activation of the farnesoid X receptor	Significant fibrosis improvement (≥ 1 stage in clinical trials)	Modest reduction in steatosis	Weight neutral	Potential worsening of the lipid profile ($\uparrow$ LDL-C)	Not demonstrated	Pruritus and dyslipidemia; safety concerns have prevented approval

PPAR), agents targeting lipid and glucose metabolism, and compounds with antifibrotic activity, achieve clinically meaningful reductions in hepatic necroinflammatory activity and, in selected subgroups, induce fibrosis regression.

The marked biological and clinical heterogeneity of MASLD/MASH limits the broad generalizability of trial findings, highlighting the need for precision medicine strategies based on metabolic phenotypes, genetic profiles, and validated noninvasive biomarkers. In addition, questions remain regarding the durability of therapeutic response, long-term safety, and the actual impact on adverse clinical outcomes such as hepatic

decompensation, hepatocellular carcinoma, and all-cause mortality.

Author contributions: Conceptualization, Formal analysis, Investigation, Project administration, Software, Visualization, Writing – original draft: EPA. Data curation, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – review & editing: JJF.

Conflicts of interest: The authors declare no conflicts of interest related to the content of this article.

Funding: The authors declare that this study received no external funding.

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