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Review Article

Breakthrough in the Treatment of Metabolic Associated Steatotic Liver Disease: Is it all over?

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ABSTRACT

On March 14, 2024, after more than 25 years of intense research and a long series of failures, the Food and Drug Administration approved resmetirom as first drug for the treatment of non-alcoholic steatohepatitis (NASH) with fibrosis (now Metabolic-Associated Steatotic Liver Disease – MASLD). The present review covers this difficult process, finally providing a drug to complement lifestyle intervention, that has long been the sole approved therapeutic intervention. However, the availability of a drug shown to reduce disease progression in advanced stages of diseases opens a series of questions that deserve even more intense research. How to continue ongoing trials? How to generate an appropriate use of resmetirom in the community, limiting treatment according to predefined criteria and according to individual risk assessment? How to guarantee that both hepatic and non-hepatic comorbidities are appropriately targeted? How to define cost-effective strategies that might prevent the generation of unacceptable differences within the population, given the high costs of novel drugs and the extremely high numbers of candidates to treatment? Only a close surveillance of drug use in the real world, generated by insurance databases and national healthcare system registries, might provide adequate answers to these compelling questions.

1. Introduction

March 14, 2024 signs a historical turning point in the treatment of metabolic-associated steatotic liver disease (MASLD). The Food and Drug Administration (FDA) approved resmetirom (Rezdiffra™) for the treatment of patients with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis. This remarks the achievement of a target long-pursued by the scientific community to reduce the progression of steatotic liver disease and the disease burden for a large fraction of adults worldwide. More than 40 years after the original description by Ludwig et al [1], several treatment failures and several billion dollars invested by pharmaceutical companies, we finally have a "magic bullet" able to fulfill the two outcomes dictated by International agencies, i.e., a) NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score (NAS) by ≥2 points) with no worsening of fibrosis; and b) an improvement in fibrosis by at least one stage with no worsening of NAS. Outcomes should be achieved without significant side-effects, which created an obstacle for approval. To comply with safety concerns, in January 2021 the FDA requirements included a possible, alternative regulatory pathway for drug approval [2]. This novel pathway requires two phase 3 randomized controlled trials (RCTs): one in NASH population without cirrhosis with liver histology as primary outcome, the second in compensated NASH cirrhosis, having adverse liver outcomes as endpoint. If both efficacy and safety are fulfilled, full approval is granted without the need for a confirmatory phase 4 trial.

The present approval is expected to have a tremendous impact on current and future trials. The present review is intended to trace the history of treatment, with hints to the future and to changing practices induced by the new achievements.

2. A summary of the epidemiological scenario

Most recent estimates indicate that the overall global prevalence of MASLD in adults is 30-38% [3,4], with differences in relation to strategies to define liver fat (biomarkers, ultrasonography). It increased by 50% between 1990-2006 and 2016-2019 [4], driven by the epidemics of diabesity and globesity [5], affecting

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all countries and spreading to areas where obesity was rare. The worldwide prevalence of NASH is more difficult to define, given the need of liver biopsy that generates a selection bias. In general, depending on the association with obesity and diabetes, it is reported around 60% in cases with indication for biopsy and between 6-30% in those without [6]. The critical characteristics determining liver disease progression is however fibrosis, which can be confidently determined by transient elastography (TE); in the community, advanced fibrosis (≥F3) is diagnosed in 6.5% of NAFLD cases, but the rate increases progressively from 3.7% in the absence of metabolic risk factors to 36.3% in the presence of multiple comorbidities [7] and 40% of NAFLD have significant fibrosis (≥ F2) [8]. From a pathogenic perspective, necroinflammation (NASH) generates fibrosis, consistently associated with long-term outcomes [9]. This explains the focus given to necroinflammation and fibrosis in therapeutic trials, with scarce interest to changes in liver fat accumulation.

3. Literature search and data extraction

A rapid search for clinical trials using the quest string "(NAFLD OR steatosis OR NASH) AND trial" on March 28, 2024 provided 3,412 studies in PubMed with 200-250 studies/year in the past 5 years. The addition of term "(drug OR pharmacologic)" limits the number to 2,098. Accordingly, the present analysis is not expected to be exhaustive, but will only focus on the most important drugs tested along the years, as well as on the issues generated by resmetirom approval.

4. MASLD drug treatment

The most important studies carried out with the use of drugs targeting completely different pathogenic mechanisms are summarized in Table 1. They cover a period of approximately 25 years of intense research, characterized by multiple failures, as detailed below. The total number of patients enrolled in the multiple RCTs is exceedingly large, including over 17,000 patients and probably two or three times as many screened around the world. The tested drugs cover several pathophysiological mechanisms, from insulin resistance to lipid metabolism and finally fibrosis, which makes it difficult to classify them into precise categories, but a few may be identified.

4.1. Insulin sensitizers (Metformin and Peroxisome-proliferator-activated receptor agonists - PPARs)

Metformin was the drug initially tested in a limited number of studies, both in the presence and in the absence of type 2 diabetes. Despite its effectiveness in reducing liver enzymes, and initial positive remarks, a meta-analysis, based on a limited number of individual patient data, did not report any significant effect on histology [10] and the drug is not recommended by International guidelines.

Tiazolidinediones (PPAR-γ agonists) were more extensively investigated because of their efficacy in redistributing the adipose tissue between the subcutaneous and the abdominal area. Whereas rosiglitazone was soon abandoned due to side effects, pioglitazone has received a lot of attention and was demonstrated to reduce both NASH severity and fibrosis. In a frequently quoted meta-analysis of 5 studies (392 patients), pioglitazone was reported to reduce histologically-detected fibrosis and promote NASH resolution, also in the presence of advanced fibrosis [11], irrespective of the presence of diabetes; this made pioglitazone one of the very few drugs suggested for use in International guidelines. Unfortunately, no individual patient meta-analysis could produce data on the possible achievement of the two criteria required by regulatory agencies in order to receive formal approval. Its use was limited by side effects, in particular by the modest increase in body weight and concerns in the presence of heart failure.

A totally different, novel approach with pioglitazone is the use of an enantiomer of deuterium-stabilized R-pioglitazone, lacking the PPAR-γ activity responsible for side-effects (namely, weight gain), but maintaining its efficacy on the liver. In a proof-of-concept study in fibrotic NASH with diabetes, the drug proved its efficacy in reducing liver fat, but also several secondary outcomes on fibrosis biomarkers and histology were reached in a higher proportion with the experimental drug at different dosage [12]. The study has not so far been extended.

Azemiglitazone (MSDC-0602K) is another PPAR-γ agonist interacting with the mitochondrial pyruvate carrier with low side effects. In a phase 2 study in NASH with F1-F3 fibrosis, at different doses, it did not meet the primary target of NAS reduction without worsening of fibrosis, but produced several metabolic effects [13]. A phase 3 study was planned [NCT03970031], but did never start.

Elafibranor, a PPAR-α/δ agonist with an intense activity on triglycerides, reported partially positive results in a phase-2 multicenter study, improving NASH without worsening of fibrosis particularly in subjects with mild disease [14]. The phase 3 registration study (RESOLVE-IT) was initiated, but an interim analysis at week 72 showed that elafibranor failed both the primary end-point (NASH resolution without worsening of fibrosis) and the key secondary end-point (fibrosis improvement by at least by one stage) [15]. Accordingly, the study was terminated.

Lanifibranor is a pan-PPAR agonist (PPAR-$\alpha/\beta/\gamma/\delta$ agonist) with key regulatory functions in metabolism, inflammation, and fibrogenesis and activity far superior to single or dual PPARs. In a phase 2 study, treatment with lanifibranor was superior to placebo for both resolution of NASH without worsening of fibrosis and improvement in fibrosis by at least one stage without worsening of NASH. A third outcome was also fulfilled, i.e., resolution of NASH plus improvement in fibrosis [16]. The study was expected to terminate recruitment in the first trimester 2024, but enrolment was paused in February 2024 due a serious treatment-related event. Final results were expected by the end of 2025, but might be retarded.

Two more PPARs deserve mention: saroglitazar and seladelpar. Saroglitazar, a PPAR-α/γ agonist, was initially tested in NASH patients in a phase 2 study having ALT levels as primary outcome and hepatic fat on MRI, insulin resistance, and dyslipidemia as secondary outcomes [NCT03061721] [17]. Safety and efficacy prompted to initiate a phase 2b study in 240 cases of NASH with fibrosis [NCT0501130], having NASH resolution and no worsening of fibrosis at 52weeks as primary outcome. The results are expected by the end 2025. Seladelpar, a selective PPAR-δ agonist shown to regulate critical metabolic and liver disease pathways, was tested in a phase 2 study in 181 NASH cases with liver fat assessed by magnetic resonance imaging proton density fat fraction (MRI-PDFF) as primary outcome at week 12 and histology at week 52 [NCT03551522]. Due to failure in primary outcome, the study was terminated and drug development was successfully continued in the area of primary biliary cholangitis [18].

4.2. Lipid mediators

Vitamin E has long been used for its antioxidant properties in NAFLD, particularly in pediatric NAFLD. In adult NASH, the clinical use of vitamin E is supported by the PIVENS study, where it proved to be superior to both placebo and pioglitazone in decreasing liver fat and necroinflammation, without significant effects on fibrosis [19]. Also in the pediatric TONIC trial, vitamin E treatment produced NASH resolution in a significantly higher

Table 1
Principal studies of pharmacologic treatment in adult patients with MASLD. Only RCT with histologic outcomes and those that paved the way to liver biopsy studies are reported, together with meta-analyses of drug classes.

Study drug (Ref) [ClinicalTrials.gov]	Study type/N. of cases Duration/Control*	Outcomes^	Most relevant results
Metformin [10]	Meta-analysis 4 RCTs 126 NAFLD cases 4-12 months	Effectiveness of metformin on liver enzymes Effects on histology (paired biopsies in a limited number of cases)	Metformin improved biochemical liver markers; no systematic improvement in liver histology
Pioglitazone [11]	Meta-analysis 5 RCTs 392 NASH cases 6-24 months	Co-primary: Improvement in advanced fibrosis (stage F3-F4) on liver biopsy; ≥1-point improvement in fibrosis of any NASH stage and NASH resolution	Improvement from F3-F4 to F0-F2: all cases, OR 4.53 (1.52-13.52); limited to advanced fibrosis, OR 10.17 (2.83-36.54); Improvement ≥1 stage: 1.77 (1.15-2.72; NASH resolution: 3.65 (2.32-5.74)
Deuterated Pioglitazone [12] [NCT04321343]	Phase 2 RCT fibrotic NASH + T2DM 117 cases 36 weeks	Primary: Percent change in liver fat content (MRI-PDFF) Secondary: - ≥ 2 points NAS improvement, no worsening of fibrosis - Many other outcomes for NASH resolution, no fibrosis worsening	Primary outcome: LSMs from baseline, -16% to -22% with different doses NASH resolution with ≥1 stage fibrosis improvement: OR 3.26 (0.63-17.21), OR 2.65 (0.48-14.63), OR 0.70 (0.12-4.18) with different doses.
Azemiglitazone [13] [NCT02784444]	Phase 2 RCT 392 F1-F3 NASH cases 12 months	Primary: ≥ 2 points NAS improvement, no worsening of fibrosis Secondary: - Any NAS improvement, no worsening of fibrosis - NASH resolution, several metabolic end-points	Primary end-point at highest dose: OR 1.64 (0.83-3.27) Significant reductions in glucose, HbA1c, insulin, liver enzymes and NAS vs. PL
Elafibranor [14] [NCT01694849]	Phase 2 RCT 275 Participants 3 years	Primary: NASH resolution without worsening of fibrosis Secondary: - changes in NAS (also including a 2-point decrease) - improvements in steatosis, ballooning, inflammation, fibrosis and surrogate markers of insulin resistance; safety and tolerability	Primary outcome: OR 2.31 (1.02-5.24), based on a modified definition In moderate or severe NASH, OR 3.18 (1.22-8.13) The predefined end point was not met in the intention to treat population
Elafibranor [15] [NCT02704403]	Phase 3 RCT 2,157 Participants 4 years	Primary: Resolution of NASH without worsening of fibrosis; time to long-term outcome Secondary: - Improvement of fibrosis of at least 1 stage; change in metabolic parameters in the presence/absence of diabetes	Cases who met primary outcome: Experimental, 138/717 (19.2%), Placebo, 52/353 (14.7%); P =0.066 Secondary endpoint on fibrosis: 176/717 (24.5%) vs. 79/353 (22.4%), P = ns
Lanifibranor [16] [NCT03008070]	Phase 2 dose-finding RCT 247 Participants 3 years	Primary: Decrease of SAF score ≥2 points, no worsening of fibrosis Secondary: - NASH resolution, no worsening of fibrosis - Improvement of fibrosis ≥1 stage and no worsening of NASH - ≥2-point NAS reduction, NASH resolution and a composite end point - Changes in enzymes, metabolic parameters, collagen turnover.	Primary outcome: Lanifibranor 1200 mg, OR 1.69 (1.22-2.34) NASH resolution, no worsening of fibrosis: OR 1.70 (1.07-2.71) and OR 2.20 (1.49-3.26) with larger dose Composite end-point: OR 2.57 (1.20-5.51) and OR 3.95 (2.03-7.66), respectively.
Vitamin E [19] [NCT00063622]	Phase 3 RCT 247 Participants 4 years vs. PL/pioglitazone	Primary: Improvement in NAFLD activity defined by change in standardized scoring of liver biopsies Secondary: - Improvement in histology components and NASH	Vitamin E significantly better than placebo in NASH improvement (43% vs. 19%, P = 0.001) No improvement in fibrosis scores
Ursodeoxycholic acid [21]	Phase 3 RCT 166 NASH patients 2 years	Primary: Response rate in NAFLD activity defined by change in scoring of liver biopsies Secondary: - Improvement in liver enzymes and body weight	Significant improvement in the degree of steatosis in UDCA and in PL. No differences in NAS or fibrosis. No difference in body weight and improvement of liver enzymes in both groups
Ursodeoxyxholic acid [22]	Phase 3 RCT vs. Vitamin E or PL 40 NASH cases 2 years	Primary: Response rate in histology by scoring of paired biopsies Secondary: - Improvement in liver enzymes	Primary outcome: NAS was unchanged in the P/P and UDCA/P groups, but imporoved in the UDCA/ Vit E group, driven by regression of steatosis Liver enzymes improved in the UDCA/ Vit E group
High-dose ursodeoxycholic acid [23]	Phase 3 RCT 186 NASH cases 18 years	Primary: Overall improvement in liver histology by paired biopsies Secondary: - Improvement in individual histology components - Improvement in liver biochemistry and body weight	The study did not meet primary outcomes. Only lobular inflammation improved, particularly in cases with elevated NAS score. Fibrosis did not change. No change in liver biochemistry
Aramchol [25] [NCT02279524]	Phase 2b RCT 247 Participants 3 years	Primary: Change from baseline in liver enzymes Secondary: - Change in liver fat (MRI-PDFF) and in liver stiffness (MRE)	Primary end-point was not met MRI-PDFF diff -4.7% (-2% to -7.5%) MRE ≥ 15%: 8.3% and 6.4% vs. 21.1% (PL)

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Table 1 (*continued*)

Study drug (Ref) [ClinicalTrials.gov]	Study type/N. of cases Duration/Control*	Outcomes*	Most relevant results
Obeticholic acid [27] [NCT01265498]	Phase 2 RCT 283 Participants 3 years	Primary: Improvement in NAFLD activity score ≥2 points Secondary: - Resolution of NASH - Change in NAS score; improvement in individual histology items - Changes liver enzymes, HOMA-IR, anthropometric measures), and health-related quality-of-life scores	Primary outcome: RR 1.9 (1.3-2.8) NASH resolution: RR 1.5 (0.9-2.6) Change in NAS: RR -0.9 (-1.3 to -0.5) Improvement in fibrosis (RR 1.8 (1.1-2.7)), ballooning (RR 1.5 (1.0-2.1)), steatosis (RR 1.7 (1.2-2.3)) and lobular inflammation (RR 1.6 (1.1-2.2))
Obeticholic acid [28] [NCT02548351]	Phase 3 RCT 1,968 participants 8 years (interim analysis)	Primary: Fibrosis improvement, no NASH worsening; NASH resolution without worsening of fibrosis Secondary: - Improvement of NASH and NAS	Primary outcome: Fibrosis improvement was: RR 1.5 (1.0-2.2) and 1.9 (1.4-2.8) with ascending dose. NASH resolution was not met (RR 1.5 (0.9-2.4) and 1.4 (0.9-2.3), respectively; high rates of TEAEs
Denifanstat [31] [NCT03938246]	Phase 2a RCT 99 F1-F3 NASH cases 12 weeks	Primary: Safety and relative change in MRI-PDFF Secondary: - Change in MRI-PDFF ≥30% - Change in NASH and FIB-4 index	Primary outcome: Liver fat decreased in a dose-dependent manner: LSMD -15.5% (-31.3-0.02) and -28.0% (-44.5 to -11.6%), 5mg and 50mg, respectively Pro-inflammatory and fibrotic markers also improved
Emricasan [32] [NCT02686762]	Phase 2 RCT 318 F1-F3 NASH cases 72 weeks	Primary: ≥ 1 fibrosis stage improvement, no NASH worsening Secondary: - Any NAS improvement, no worsening of fibrosis, NASH resolution	Primary outcome: There was a trend in favor of placebo (21.5% vs. 13.7% and 13.4% vs. emricasan 5 mg and 50 mg groups)
Simtuzumab [33] [NCT01672866 and NCT01672879]	Two Phase 2 RCTs bridging fibrosis, 219 cases; cirrhosis, 258 96 weeks	Primary: Change in hepatic collagen content, measured by morphometry in bridging fibrosis, change in HVPG in cirrhosis Secondary: - Progression to cirrhosis in bridging fibrosis, events in cirrhosis	Hepatic collagen content decreased similarly in drug- and PL-treated groups No difference in HVPG between groups Studies were discontinued earlier than the planned 240 weeks for TEAEs and treatment failure
Selonsertib [34] [NCT03053050 and NCT03053063]	Two Phase 3 RCTs 803 NASH with F3 fibrosis, 877 with cirrhosis 12 months vs. simtuzumab	Primary: ≥1 stage improvement in fibrosis, no NASH worsening for both studies Secondary: - ≥1-stage improvement in fibrosis; proportion with NASH resolution - proportion of patients with progression to cirrhosis (from F3 fibrosis)	Fibrosis F3: Primary outcome in 10% and 12% with study drug at different dose, 13% with PL. No differences in progression to cirrhosis Cirrhosis: Primary outcome in 14%, 13% and 13%, respectively. No differences in the risk of liver-related events (decompensation)
Belapectin [35] [NCT02462967]	Phase 2 RCT 162 NASH cirrhosis 52 weeks	Primary: Reduced HVPG Secondary: - ≥1-stage improvement in fibrosis - Change in liver stiffness; complication of cirrhosis (decompensation)	Primary outcomes: PL, +0.10mmHg; Belapectin, -0.28 and -0.25 with the two doses (not significant) Subgroup without varices: LSM diff -2.0 (-3.7 to -0.3) and -0.7 (-2.4 to +1.0)
Cenicriviroc [36] [NCT02217475]	Phase 2b RCT 289 participants 3 years	Primary: NAS improvement ≥2 points with ≥1-point reduction in either lobular inflammation or ballooning, no worsening of fibrosis Secondary: - Complete resolution NASH, no worsening of fibrosis stage - Safety and tolerability; change in liver biochemistry and fasting metabolic parameters	Primary end-point: OR 0.82 (0.44-1.52) NASH resolution: OR 2.20 (1.11-4.35) No safety concerns
Cenicriviroc [37] [NCT02217475]	Phase 2 RCT 289 participants at year 2 3 years	Primary: NAS improvement by ≥2 points with ≥1-point reduction in either lobular inflammation or ballooning, no worsening of fibrosis Secondary: - Complete resolution of NASH, no worsening of fibrosis at different time points - Adverse events, eventually leading to withdrawal, changes in non-invasive markers and scores of fibrosis, weight, anthropometry	Fibrosis improvement ≥1 stage, no NASH worsening: OR 2.03 (0.89-4.62) No systematic differences between study groups in main outcome measures
Cenicriviroc [38] [NCT03028740]	Phase 3 RCT 1,778 participants 4 years	Primary: improvement in fibrosis by ≥1 stage and no worsening of NASH; time to first occurrence of adjudicated events. Secondary: - Fibrosis improvement ≥2 stages; NASH resolution, no worsening of fibrosis at different time points	Primary end-point: OR 0.84 (0.63-1.10) NASH resolution: 23.0% vs. 27.2% in PL TEAE similar in the two groups
Liragluitide [39] [NCT01237119]	Phase 2 RCT 52 Participants 4 years	Primary: NASH resolution, no worsening of fibrosis Secondary: - Improvement in NAS and its individual components - Changes in liver enzymes and drug safety	Primary outcome: RR 4.3 (1.0-17.7) NAS score improvement: RR 1.2 (0.8-1.7) Improvement in fibrosis: RR 1.9 (0.5-6.7) No differences in ALT and AST

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Table 1 (*continued*)

Study drug (Ref) [ClinicalTrials.gov]	Study type/N. of cases Duration/Control*	Outcomes^	Most relevant results
Semaglutide [40] [NCT02970942]	Phase 2 RCT 320 Participants 4 years	Primary: Resolution of NASH, no worsening of fibrosis Secondary: - Improvement ≥1 fibrosis stage and no worsening of NASH - Change in fibrosis stage, NAS and score components - Changes in liver enzyme levels, ELF, liver stiffness and CAP, body - weight, glucose metabolism, blood pressure, and lipid levels	NASH resolution at 0.4-mg: OR 6.9 (2.6-17.6); fibrosis improvement: 1.4 (0.6-3.3) Percent decrease in body weight: up to 12.5% with ascending dose No differences in liver enzymes and ELF. Moderate increase in amylase and lipase
GLP-1 RAs [42]	Meta-analysis 1,454 patients	Changes in hepatic steatosis and fibrosis markers Changes in liver function test Changes in metabolic parameters and body composition	Steatosis: SMD -1.05 (-1.62 to -0.48) Fibrosis: SMD APRI -0.68 (-1.24 to -0.18)
Tirzepatide [NCT04166773]	Phase 2 RCT 196 participants 5 years	Primary: absence of NASH, no worsening of fibrosis Secondary: - Percentage with ≥1 point decrease in fibrosis, no NASH worsening - ≥2 point decrease in NAS, in liver fat by MRI-PDFF and body weight	No interim data available
Cotadutide [45] [NCT03235050]	Phase 2b RCT vs. liraglutide or PL 834 T2DM patients 14 weeks	Primary: changes in HbA1c and body weight Secondary: - Percent reaching HbA1c target; weight loss ≥ 5% - Liver enzymes, non-invasive biomarkers of steatosis and fibrosis	Efficacy in primary end-points similar to liraglutide Larger efficacy on liver enzymes vs. liraglutide, but similar changes in both FIB-4 and NFS markers of fibrosis
SGLT-2 inhibitors [46]	Meta-analysis Six studies 850 T2DM patients 12 months	Primary: changes in liver enzyme levels and liver fat content on imaging techniques.	ALT: WMD -10.0 U/L (-12.2 to -7.79) GGT: WMD -14.5 U/L (-19.3 to -9.6) Liver fat on MRI: WMD -2.05 (-2.61 to –1.48). No biopsy data
Aldafermin [47] [NCT02443116]	Phase 2 RCT, NAS ≥4, fibrosis F2-3 78 cases 24 weeks	Primary: Absolute change in liver fat content (MRI-PDFF) Secondary: - Improvement in serum markers and histologic measures of fibrosis	Liver Fat content: WMD -5% (-8.0% to -1.9%). Fibrosis improvement ≥ 1 stage) with no worsening of NASH was achieved in 38% vs 18% in PL (P = 0.10)
Efruxifermin [48] [NCT03976401]	Phase 2a RCT, NAS ≥4, fibrosis F2-3 80 patients 24 weeks	Primary: Absolute change in liver fat content (MRI-PDFF) Secondary: - Improvement in liver enzymes and non-invasive markers	Primary outcome: met in all study groups at different doses Limited biopsy data available in PL
Efruxifermin [49] [NCT04767529]	Phase 2b RCT, NAS ≥4, fibrosis F2-3 128 patients 24 weeks	Primary: Fibrosis improvement by ≥ 1 stage, no NASH worsening; NASH resolution no fibrosis worsening Secondary: - Any NASH resolution, ≥1 stage fibrosis improvement - Change in MRI-PDFF, change in non-invasive markers	Primary outcomes: RR 2.3 (1.1.-4.8) and 2.2 (1.0-5.0) with ascending dose NASH resolution: RR 3.1 (1.4-6.9) and 5.2 (2.4-11.1)
Pegozafermin [50] [NCT04929483]	Phase 2b F2-F3 RCT 222 cases 24 weeks	Primary: Percent with fibrosis improvement by ≥ 1 stage, no NASH worsening; percent with NASH resolution no fibrosis worsening Secondary: - NASH resolution, proportion with fibrosis improvement ≥1 stage - Change in MRI-PDFF, change in non-invasive markers	Primary outcomes: Differences in fibrosis improvement 14% (-9 to 38); 19% (5-32) and 20% (5-35) with ascending dose; differences in NASH resolution: 35% (10-59), 21% (9-33) and 24% (10-37), respectively
Resmetirom [51] [NCT02912260]	Phase 2 NASH RCT, fibrosis F1-F3 348 cases 36 weeks	Primary: Relative change in liver fat (MRI-PDFF) Secondary: - ≥2-point NAS improvement; NASH resolution without fibrosis worsening - Changes in liver enzymes, safety	Primary outcomes: LQD -28.8% (-42.0% to -15.7%) Moderate changes in histology Liver fibrosis (ELF score): -0.48 (-0.99 to -0.09) No safety concerns (mild diarrhea)
Resmetirom [52] [NCT0419749]	Phase 3 combined RCTs 972 NASH cases 52 weeks	Primary: Incidence of TEAE Secondary: - Lipid levels; hepatic fat content (MRI-PDFF); NASH biomarkers - Changes in liver stiffness ≥ 2kPa (VCTE) or at MRE	Primary: no safety concerns A much larger proportion of cases improved by ≥ kPa (VCTE) or by MRE, and a lower proportion had fibrosis worsening
Resmetirom [53] [NCT03900429]	Phase 3 RCT 966 NASH cases, fibrosis F1-F3 52 weeks	Primary: NASH resolution (including a reduction in NAS score by ≥2 points) with no worsening of fibrosis; improvement in fibrosis by ≥ 1 stage, no NAS worsening Secondary: - Percent change in lipids, adverse events, biochemical data	Primary end-points: they were all met with both doses (80 and 100 mg) Both NASH resolution and fibrosis improvement: 80mg, WMD 9.5 (5.4-13.6); 100mg, WMD 11.6 (7.5-15.8)

Abbreviations: ALT-AST, alanine and aspartate transaminases; APRI, AST/platelet ratio index; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; FIB-4, fibrosis 4 index; GGT, γ-glutamyl transpeptidase; HbA1c, glycosylated A1c hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; HVPG, hepatic venous pressure gradient; LSM, least square mean; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; LQD, least square difference; NAS, nonalcoholic activity score; NFS, NAFLD fibrosis score; OR, odds ratio; PL, placebo; RCT, randomized controlled study; RR, relative risk; SAF, steatosis, activity, fibrosis; SMD, standardized mean difference; TEAE, treatment emergent adverse events; UDCA, ursodooxycholic acid; VCTE, vibration-controlled transient elastography; Vit E, vitamin E; WMD, weighed mean difference.

* For RCTs, comparator is placebo (PL), unless otherwise reported.

^ Outcomes assessed by liver biopsy, unless otherwise reported

proportion of cases vs. placebo, again with no effects on fibrosis [20], and treatment remains an option in international pediatric guidelines.

Ursodeoxycholic acid treatment has been extensively investigated, given its anti-apopototic and anti-oxidant properties. Three trials based on liver biopsy provided evidence of some effects on steatosis, but no evidence was retrieved for a beneficial effect on fibrosis [21-23], as well as on fibrosis biomarkers when tested at higher doses [24].

Aramchol is a conjugate of cholic and arachidic acid that was shown to reduce de novo lipogenesis in animal models. In humans, it was tested on NAFLD patients (predominantly, non-NASH) in a phase 2b study (ARREST), having hepatic triglycerides by magnetic resonance spectroscopy as primary end-point, and the changes in liver histology required by FDA as secondary end-points [25]. The study failed the primary end-point at 52-week analysis, but fulfilled the secondary end-points and is still ongoing as a larger phase 3 study (ARMOR study), expected to be completed in June 2027.

Obeticholic acid (OCA) is a semisynthetic derivative of the primary human bile acid chenodeoxycholic acid, the natural agonist of the farnesoid X receptor (FXR), that received approval for the treatment of primary biliary cholangitis. The compound was originally tested for NASH treatment against placebo in a phase 2, proof-of-concept study, where it reduced the markers of liver inflammation, together with significant metabolic effects on insulin sensitivity [26]. The much larger phase 2 FLINT study, supported by interim analyses, confirmed the positive effects on liver histology, but provided a larger evidence of side effects (pruritus and increased cholesterol levels) frequently requiring discontinuation or additional statin treatment [27]. An even larger phase 3 study (REGENERATE) was initiated, with conflicting results at interim analyses [28]. The pharma company requested approval for NASH treatment (as already given in primary biliary cholangitis), but FDA required additional safety analyses and a longer study period for concerns over the drug modest efficacy and the range of safety problems. Accordingly, the company decided to discontinue the NASH-related trial.

Another FXR ligand, EDP-305, 15 times more potent than OCA, has been so far tested in a phase 2 study (NCT03421431) with impressive results on liver fat, but no histology data are available on necroinflammation and fibrosis [29]. No additional studies were retrieved in ClinicalTrials.gov.

Volixibat is an inhibitor of the apical sodium-dependent bile acid transporter, expected to improve NASH by blocking bile acid reuptake and stimulating hepatic bile acid production. The drug was tested in 197 patients without cirrhosis in a phase 2, dose finding study [NCT02787304]. The primary outcome was a ≥2-point reduction in NAS without fibrosis worsening at week 48, but two predefined interim endpoints at week 24 (≥5% reduction in MRI-PDFF and ≥20% decrease in ALT) were not fulfilled; the study was terminated [30], but remained under development for cholestatic pruritus.

Denifanstat, an orally-active, potent inhibitor of fatty acid synthase under development in cancer therapy, is under investigation in NASH patients (FASCINATE program). The initial phase 2 RCT [NCT04906421] met the primary outcomes of changes in liver fat and liver enzymes, and provided some clues to histology improvements [31]. A second study [NCT03938246] has been completed in NASH patients with fibrosis F2-F3, aimed at primarily testing changes in NAS score and fibrosis, according to FDA rules. Data are expected soon.

Other drugs under investigation, directly or indirectly acting on steatosis are rencofilstat, a cyclosporine analog targeting the effects of steatosis on oxidative stress, icosabutate, a long-chain fatty acid, and nor-ursodeoxycholic acid.

4.3. Anti-fibrotic agents

Emricasan, a pan-caspase inhibitor was hypothesized to reduce fibrosis by reducing apoptosis and cytokine generation, but failed the primary end-point in a study in NASH patients with fibrosis F1-F3, with a trend in favor of placebo [32].

Similarly, simtuzumab, a monoclonal antibody against lysyl-oxidase 2, completely failed two phase 2 studies in bridging fibrosis and in compensated cirrhosis [33]. It did not produce any effect on histology compared with placebo or did not reduce hepatic venous pressure gradients (HVPG) and events in cirrhosis.

Selonsertib, a selective inhibitor of apoptosis signal-regulating kinase 1, expected to play a role in inflammation and fibrosis, was initially tested in two phase 2 studies of NASH patients with fibrosis F2-F3 [NCT01672866 and NCT01672879], and in combination with simtuzumab [NCT02466516]. It did not meet the expected results on fibrosis, but was nonetheless moved into two phase 3 studies of NASH with/without cirrhosis where it did not lead to fibrosis regression or reduce disease progression in comparison with placebo [34].

Belapectin, an inhibitor of galectin-3 administered via biweekly injections, was tested in a phase 2 study of NASH cirrhosis with portal hypertension, having change in HVPG as primary outcome and change in histology as secondary outcomes [35]. The drug did not reach the primary outcome, but reduced progression in subjects without varices.

Cenicriviroc is a dual antagonist targeting the chemokine receptor 2 and 5 (CCR2/5) tested for treating liver fibrosis. In the CENTAUR phase 2b trial, cenicriviroc treatment for one year failed to improve NAS by ≥ 2 points without worsening of fibrosis, but met the secondary fibrosis end-point (improvement of fibrosis, no NASH worsening) [36]. Continued two-year treatment corroborated the initial results of significant effects on fibrosis, with greater effects in subjects with advanced fibrosis [37]. The long-term effects of cenicriviroc, investigated in a large phase 3 placebo-controlled trial (AURORA), were recently reported and the primary outcome of fibrosis improvement was not met [38].

4.4. Drugs primarily acting on glucose metabolism and body weight

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), double and triple agonists have been extensively investigated, given their impressive activity on glucose metabolism and body weight.

Liraglutide was the first GLP-1RA tested for efficacy on NASH patients. In the phase 2 LEAN study, conducted in a very limited number of cases, liraglutide, at a dose of 1.8 mg daily, promoted a higher rate of NASH resolution compared with placebo and a lower rate of fibrosis progression, warranting more extensive studies [39]. However, the registration process was stopped in favor of semaglutide, a weekly-dosing compound with more pronounced metabolic effects proved to be much superior to liraglutide on weight loss outcomes. In the phase 2b study, semaglutide at the daily dose of 0.1, 0.2 and 0.4 mg significantly achieved NASH resolution compared with placebo, but failed to improve the fibrosis stage, irrespective of treatment dose [40]. Data are not available so far on liver disease progression at the weekly dosage of 2.4 mg, that produced a massive weight loss [41] and has received approval as anti-obesity drug. To cover this gap, the phase 3 ESSENCE study [NCT04822181] is going to test the effects of 2.4mg semaglutide vs. placebo at 72 weeks in 1,200 participants on the classical primary outcomes of NASH resolution and fibrosis improvement, together with an additional primary outcome of cirrhosis-free survival after 240 weeks of treatment. Secondary outcomes will include different effects on NASH and fibrosis, as well as changes in body weight, liver enzyme levels, liver stiffness and steatosis, glucose metabolism, blood pressure, and blood lipids, but also major

adverse cardiovascular events (MACEs) and cardio-hepatic event-free survival. Final data are expected by 2029. Another study will test the combination of weekly semaglutide combined with 3 different doses of NNC0194-0499, a fibroblast growth factor-21 modulator (see below) or cagrilintide in a phase 2, dose-finding study. Outcomes will include safety and effectiveness on NASH and fibrosis, as well as on individual NAS features. The oral formulation of semaglutide has so far received scarce interest in MASLD area.

In a meta-analysis covering 5 RCTs and comprising 1,454 NASH patients, GLP-1RAs were demonstrated to decrease hepatic fat content, liver biochemistry and inflammatory markers but changes in fibrosis parameters, although improved, did not reach statistical significance [42].

Another drug, tirzepatide, a subcutaneous, weekly-dosing double agonist targeting both GLP-1 and the gastric inhibitory polypeptide is actively being tested in MASLD patients vs. placebo in a phase 2 study (NCT04166773). The final results are soon expected. Also this drug was highly effective in promoting a massive weight loss, ranging up to 20.9% after 72 weeks with the higher dosage [43], with a safety profile not affected by liver impairment [44].

The dual GLP-1 and glucagon receptor agonist cotadutide is similarly under investigation in a phase 2, proof-of-concept study (NCT05364931), expected to provide the final results in the next few months. In another phase 2b study in patients with type 2 diabetes the drug showed effects on weight loss comparable or superior to those achieved with liraglutide 1.8 mg [45] and similar effects on fibrosis biomarkers.

Sodium-glucose cotransporter-2 inhibitors (SGLT-2Is) are a relatively-new class antidiabetic medications, that received increasing interest for a possible use in patients with type 2 diabetes and liver disease. They promote glucose excretion in the urine, thus improving the metabolic milieu and reducing body weight. A meta-analysis covering the literature to October 2020 failed to retrieve studies based on paired liver biopsies. According to the review, including 6 studies testing dapagliflozin, 3 empagliflozin and 3 canagliflozin, SGLT-2I treatment reduces liver enzymes and liver fat, based on magnetic resonance techniques, compared with placebo [46]. Only real-world data are available on possible changes in inflammatory and fibrotic activity, based on surrogate biomarkers.

4.5. Fibroblast growth factor (FGF) analogs

FGF family members have broad effects on cell activity and proliferation. Aldafermin, an engineered analog of FGF19, inhibits bile acid synthesis and regulates metabolic homeostasis. It effectively reduced liver fat (MRI-PDFF) and increased the rate of fibrosis improvement and NASH resolution [47], without relevant side effects, but no more studies were planned.

Efruxifermin is a fusion protein of a human IgG linked to a modified FGF21 (Fc-FGF21), longer acting than most FGF21 analogs. It significantly reduced liver fat in a phase 2a study [48], without safety concerns. In a phase 2b study, the drug confirmed its activity on liver fat, also improving fibrosis by $\geq$1 stage in F2-F3 NASH and no NAS worsening [49]. Accordingly, the drug has been moved to two phase 3 studies [NCT06215716 and NCT06161571], expected to enroll 1,000 and 600 NASH patients with different degrees of fibrosis, to be completed in 2027 and 2026, respectively.

Pegozafermin is a pegylated FGF21 analog also tested in non-cirrhotic NASH patients. The two primary end points of fibrosis improvement without NASH worsening and NASH resolution, no fibrosis worsening, were both met at week 24 at high drug dosage [50], also supporting the progress to phase 3 trial. A very long-term phase 3 study (ENLIGHTEN-Fibrosis, planned to enroll 1,050 cases) has been registered to provide data in 2029 [NCT 06318169].

4.6. Thyroid hormone receptor-β agonist

Resmetirom, the "magic bullet", is an oral selective thyroid hormone receptor-β agonist, progressively developed for the treatment of NASH. Animal studies showed that the compound effectively reduces plasma lipids and hepatic fat, as well as apoptosis and inflammation, improves insulin sensitivity, and promotes liver regeneration. Following a proof-of-concept study where it showed efficacy in reducing liver fat by MRI-PDFF [51] and safety, it was moved to phase 3 in the MAESTRO program. The phase 3 MAESTRO-NAFLD-1 study confirmed safety, with mild diarrhea as common event, and efficacy on liver fat and fibrosis, expressed by reduced transient elastography [52]. Finally, the MAESTRO-NASH study hit both regulatory targets for NASH drug approval, and in addition it also doubled the probability to have a marked reduction of NAS score ($\geq$2 points) (additional primary end-point) [53]. This led to formal accelerated approval (along with breakthrough therapy, fast track, and priority review designations) by FDA for NASH with moderate and advanced fibrosis (stages F2-F3), while the study remains ongoing to generate confirmatory data (MAESTRO-NAFLD-OLE, NCT04951219) to verify clinical benefits and to support full approval. Another ongoing trial is testing resmetirom efficacy in preventing liver decompensation in well-compensated NASH cirrhosis versus placebo (MAESTRO-NASH-OUTCOMES, NCT05500222). The drug is expected to be available in the U.S. in April 2024. As to Europe, the authorization for marketing of resmetirom received validation from the European Medicines Agency and the formal approval is pending.

5. The alternative lifestyle/weight loss treatment

Intensive lifestyle programs promoting healthy diet, habitual physical activity and weight loss have long been used for MASLD treatment, and are supported by international [54-56] and national guidelines [57]. Recommendations are based on epidemiological studies, with only a few RCTs available and mainly addressing specific issues (Mediterranean diet, low-carb diet, habitual physical activity) [58]. Following a seminal experience showing that$\geq$ 7% weight loss reduced liver fat and necroinflammatory disease activity, not fibrosis [59], a large pivotal experience confirmed that nearly 100% of cases achieving the weight loss target of $\geq$7-10% reduce steatosis and NAS, as well as fibrosis, although their number at 1-year follow-up is only 10% [60]. These results were confirmed in a community-based cohort, and were consistent, irrespective of initial BMI [61]. Thus, lifestyle intervention to promote weight loss became mandatory in both arms of pharmacologic RCTs; this policy, in keeping with good clinical practice, increases the number of placebo-treated cases achieving therapeutic outcomes, reduces any possible advantage of drugs and is considered among the possible reasons for drug failures [62].

Behavioral interventions require dedicated teams, rarely found in liver units [63], and the engagement of asymptomatic MASLD patients in intensive lifestyle protocols [64]. eHealth technology is a possible resource to engage patients limiting space and time constraints [65], and has grown in the last decade, either as web-based approach or using dedicated apps [66], thus expanding lifestyle intervention to a much larger community [63]. The long-term (5-year) effectiveness of a web-based behavioral intervention in MASLD is similar to that achieved by group-based programs, reducing disease progression [67] and worsening of surrogate markers of steatosis and fibrosis [68]. However, the desired 10% weight loss target remains limited to approximately 10% of the initial cohort [68].

The importance of weight loss for reducing MASLD progression has also been translated into the surgical arena, where several cohort studies confirmed that bariatric surgery is able to re-

verse NASH and fibrosis. A systematic review and meta-analysis of 32 cohort studies reported 1-year resolution of steatosis in 66% of cases, inflammation in 50%, ballooning degeneration in 76%, and fibrosis in 40%, with new or worsening of fibrosis limited to 12% [69], with differences between Roux-en-Y gastric by-pass (higher effect on steatosis) and sleeve gastrectomy (higher effect on fibrosis) [70]. There is also evidence that prior bariatric surgery reduces the risk of incident cirrhosis and mortality in patients with obesity and NAFLD [71].

In the meantime, progress in the drug treatment of obesity has reached impressive results. In the STEP program, 2.4mg weekly semaglutide was reported to produce an average weight loss of 15-16% after 68 weeks [72], also improving cardiovascular and metabolic risk factors [73]. When cagrilintide was added, weight loss increased further to 17.1% of initial weight, without evidence of a plateau [74]. In the SURMOUNT program, tirzepatide 15mg reduced body weight by 20.9% after 72 weeks, and nearly 40% of cases lost 25% of their initial weight [43]. The triple agonist retatrutide (12mg weekly) produced an average weight loss of 24.2%, and 26% of cases lost ≥30% of initial body weight [75]. These drugs are not without side effects: they need slow titration to reduce gastrointestinal complaints, promote sarcopenia associated with massive weight loss, and their continued use requires lifelong observation [76]. However, daily oral agents might soon be available (orforglipron) [77], increasing acceptability and widespread use.

6. Questions for future research - Conclusion

The recent, long-awaited approval of a drug - resmetirom - for MASLD treatment has definitely closed a gap, but several clinical and ethical questions remain open for managing treatment, both in the community and in clinical trials, and are discussed below.

6.1. Should placebo-treated patients be maintained in ongoing and future trials?

The large majority of pharmacologic RCTs in MASLD have been and are being carried out comparing the experimental treatment against placebo. According to the Helsinki declaration, the use of placebo is considered ethically acceptable only in the absence of drugs of proven efficacy; maintaining patients in the placebo arm in the presence of an effective drug (resmetirom) violates the equipoise principle and expose patients to the risk of non-receiving the best available or a supposedly at least as effective treatment [78]. Accordingly, all patients should be informed that drug treatment is now available and should be invited to sign a new consent, updating the information. This is mainly the case of long-term phase 3 regulatory RCTs, frequently testing cardiovascular outcomes. The possibility also exists to move placebo-treated cases to resmetirom, in accordance with the equipoise principle, but this would jeopardize the validity of trials. Pragmatically, short-term, phase 2 studies should be completed, provided that patients sign the new consent formulation, but new RCTs should consider resmetirom as alternative treatment.

6.2. Should resmetirom be preferred to weight-losing treatment or should it be used as add-on in patients with severe grades of obesity?

Resmetirom has a modest or no significant effect on body weight, but the subgroups who lost weight in the course of active treatment in the MAESTRO program showed a greater effect on steatosis [51]. About 65-70% of enrolled patients had type 2 diabetes, and the use of GLP-1RAs was only permitted when stable by ≥ 6 months and at doses used for diabetes treatment. The important weight loss generated by high-dose single, double and triple incretin treatment, although at present not curative of MASLD, is highly appreciated by patients with severe obesity and is associated with reduced risk of cardiovascular outcomes – so far proven with semaglutide [79] – and improved quality of life [73]. In lean MASLD patients without diabetes, resmetirom becomes the treatment of choice, but in individuals with diabetes and particularly in the presence of severe obesity, patients' preferences should be considered. Incretin-induced weight loss might be preferable to MASH resolution, due to the cardiovascular risk and the relative unawareness of liver disease progression in most MASLD cases [80]. Combination treatment might be the solution, but we need appropriate research studies.

6.3. Is lifestyle intervention still an option, irrespective of treatment arm?

Lifestyle intervention procedures are cumbersome and difficult to maintain in the long-term. The future scenario of MASLD treatment might differ in relation to the severity of obesity and the presence of diabetes, where support and education for lifestyle changes should be mandatory, independently of the pharmacologic treatment of glucose abnormalities. In patients with obesity, the availability of drugs able to induce a massive weight loss – comparable to that achievable by bariatric (metabolic) surgery – is very likely to reduce motivation to spend time and money to modify food preferences and engage in physical activity, i.e., modify habitual lifestyle. When high-dose semaglutide was added to intense lifestyle intervention (STEP 3 study [81]) the final effects on weight loss were only minimally larger than those measured during the sole semaglutide treatment (STEP 1 study [41]), but in community-based treatment the effects might be different [82]. Engagement in physical activity should thus remain a constant practice at any age. During weight-loss periods, physical activity is mandatory to prevent or to reduce the negative effects of sarcopenia in liver disease progression and survival [83], whereas the adherence to the different components of healthy lifestyle *per se* reduces all-cause and cardiovascular mortality [84], in a dose-dependent manner [85].

6.4. Should all these drugs be used life-long and how to afford the costs?

No long-term study is available to define how long resmetirom should be used to indefinitely prevent progressive liver disease. Should it be used as long as complete resolution of steatosis and fibrosis occur and what happens after treatment stop? High-doses incretins determine a progressive weight loss, but weight regain invariably occurs after treatment stop [86]. Should these drugs be used at intervals, or tapered down after the achievement of a large amount of weight loss? Many more studies should be done to answer all these questions. The use of "real world" post-marketing data, registered in insurance databases, might be an important source of information.

The problem of costs is both ethical and economic: the cost of semaglutide exceeds 1,300 US $ per month. In insurance-type healthcare systems, these drugs are expected to generate unacceptable differences within the population, given that payers do not always cover costs. In the U.S., a law was initially passed to bar Medicare from covering weight loss medications after the safety concerns with the fenfluramine-phentermine combination. Later, a resolution was approved calling obesity a disease, which opens the way to reimbursement for patients at high cardiovascular risk that are either overweight or obese, given the recently approved additional indication of semaglutide for cardiovascular disease [87]. However, the high cost will progressively increase the future premium for beneficiaries, a matter of general concern. For universalistic healthcare systems, that are all suffering from insufficient

funding, the widespread prescription of these drugs in the large population who could benefit would result in a final bankruptcy.

7. Conclusion

A final question remains: Who should be responsible for treatment prescription? Again, the answer needs to be put in the context of the type of healthcare system. With a look at the universalistic Italian system, there is large consensus that MASLD should be initially screened by surrogate biomarkers and cared for by general practitioners. Patients with NASH, fibrosis or other comorbidities, should be referred to a multidisciplinary team of specialists, in order to guarantee that both hepatic and non-hepatic comorbidities are appropriately targeted. Selection of treatment will depend on a "principal risk" assessment, with the liver being the primary or co-primary target only in the presence of fibrosis, without forgetting the general need to move patients to healthier lifestyles.

Conflict of interest

MLP received a fee for participation in a Novo Nordisk advisory board. FP and GM declared no conflicts.

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References

[1] Ludwig J, Viggiano TR, McGill DB, et al. Nonalcoholic steatohepatitis: Mayo Clinic experience with an hitherto unnamed disease. Mayo Clin Proc 1980;55:434–8.
[2] Matsubayashi T. Drug development for nonalcoholic steatohepatitis (NASH) with fibrosis: a regulatory perspective. In: Available at: https://sbiaevents.com/files2/NASH-Webinar-January-2021.pdf.; 2021. p. Accessed March 28, 2024.
[3] Wong VW, Ekstedt M, Wong GL, et al. Changing epidemiology, global trends and implications for outcomes of NAFLD. J Hepatol 2023;79:842–52.
[4] Younossi ZM, Golabi P, Paik JM, et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology 2023;77:1335–47.
[5] Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11–20.
[6] Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.
[7] Petta S, Di Marco V, Pipitone RM, et al. Prevalence and severity of nonalcoholic fatty liver disease by transient elastography: Genetic and metabolic risk factors in a general population. Liver Int 2018;38:2060–8.
[8] Bazerbachi F, Haffar S, Wang Z, et al. Range of normal liver stiffness and factors associated with increased stiffness measurements in apparently healthy individuals. Clin Gastroenterol Hepatol 2019;17:54–64 e51.
[9] Mozes FE, Lee JA, Vali Y, et al. Performance of non-invasive tests and histology for the prediction of clinical outcomes in patients with non-alcoholic fatty liver disease: an individual participant data meta-analysis. Lancet Gastroenterol Hepatol 2023;8:704–13.
[10] Caldwell SH, Argo CK, Al-Osaimi AM. Therapy of NAFLD: insulin sensitizing agents. J Clin Gastroenterol 2006;40(Suppl 1):S61–6.
[11] Musso G, Cassader M, Paschetta E, et al. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: A meta-analysis. JAMA Intern Med 2017;177:633–40.
[12] Harrison SA, Thang C, Bolze S, et al. Evaluation of PXL065 - deuterium-stabilized (R)-pioglitazone in patients with NASH: A phase II randomized placebo–controlled trial (DESTINY-1). J Hepatol 2023;78:914–25.
[13] Harrison SA, Alkhouri N, Davison BA, et al. Insulin sensitizer MSDC-0602K in non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled phase IIb study. J Hepatol 2020;72:613–26.
[14] Ratziu V, Harrison SA, Francque S, et al. Elafibranor, an agonist of the peroxisome proliferator-activated receptor-alpha and -delta, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology 2016;150:1147–59 e1145.
[15] GENFIT: GENFIT: Announces results from interim analysis of RESOLVE-IT phase 3 trial of elafibranor in adults with NASH and fibrosis. In: https://www.globenewswire.com/news-release/2020/05/11/2031418/0/en/GENFIT-Announces-Results-from-Interim-Analysis-of-RESOLVE-IT-Phase-3-Trial-of-Elafibranor-in-Adults-with-NASH-and-Fibrosis.html. GlobeNewswire, 2020.
[16] Francque SM, Bedossa P, Ratziu V, et al. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. N Engl J Med 2021;385:1547–58.
[17] Gawrieh S, Noureddin M, Loo N, et al. Saroglitazar, a PPAR-alpha/gamma agonist, for treatment of NAFLD: A randomized controlled double-blind phase 2 trial. Hepatology 2021;74:1809–24.
[18] Hirschfield GM, Bowlus CL, Mayo MJ, et al. A phase 3 tial of seladelpar in primary biliary cholangitis. N Engl J Med 2024;390:783–94.
[19] Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675–85.
[20] Lavine JE, Schwimmer JB, Van Natta ML, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA 2011;305:1659–68.
[21] Lindor KD, Kowdley KV, Heathcote EJ, et al. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of a randomized trial. Hepatology 2004;39:770–8.
[22] Dufour JF, Oneta CM, Gonvers JJ, et al. Randomized placebo-controlled trial of ursodeoxycholic acid with vitamin E in nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2006;4:1537–43.
[23] Leuschner UF, Lindenthal B, Herrmann G, et al. High-dose ursodeoxycholic acid therapy for nonalcoholic steatohepatitis: a double-blind, randomized, placebo–controlled trial. Hepatology 2010;52:472–9.
[24] Ratziu V, de Ledinghen V, Oberti F, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. J Hepatol 2011;54:1011–19.
[25] Ratziu V, de Guevara L, Safadi R, et al. Aramchol in patients with nonalcoholic steatohepatitis: a randomized, double-blind, placebo-controlled phase 2b trial. Nat Med 2021;27:1825–35.
[26] Mudaliar S, Henry RR, Sanyal AJ, et al. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology 2013;145:574–82 e571.
[27] Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385:956–65.
[28] Younossi ZM, Ratziu V, Loomba R, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2019;394:2184–96.
[29] Ratziu V, Rinella ME, Neuschwander-Tetri BA, et al. EDP-305 in patients with NASH: A phase II double-blind placebo-controlled dose-ranging study. J Hepatol 2022;76:506–17.
[30] Newsome PN, Palmer M, Freilich B, et al. Volixibat in adults with non-alcoholic steatohepatitis: 24-week interim analysis from a randomized, phase II study. J Hepatol 2020;73:231–40.
[31] Loomba R, Mohseni R, Lucas KJ, et al. TVB-2640 (FASN Inhibitor) for the treatment of nonalcoholic steatohepatitis: FASCINATE-1, a randomized, placebo–controlled phase 2a trial. Gastroenterology 2021;161:1475–86.
[32] Harrison SA, Goodman Z, Jabbar A, et al. A randomized, placebo-controlled trial of emricasan in patients with NASH and F1-F3 fibrosis. J Hepatol 2019;72:816–27.
[33] Harrison SA, Abdelmalek MF, Caldwell S, et al. Simtuzumab Is ineffective for patients with bridging fibrosis or compensated cirrhosis caused by nonalcoholic steatohepatitis. Gastroenterology 2018;155:1140–53.
[34] Harrison SA, Wong VW, Okanoue T, et al. Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH: Results from randomized phase III STELLAR trials. J Hepatol 2020;73:26–39.
[35] Chalasani N, Abdelmalek MF, Garcia-Tsao G, et al. Effects of belapectin, an inhibitor of galectin-3, in patients with nonalcoholic steatohepatitis with cirrhosis and portal hypertension. Gastroenterology 2020;158:1334–45 e1335.
[36] Friedman SL, Ratziu V, Harrison SA, et al. A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. Hepatology 2018;67:1754–67.
[37] Ratziu V, Sanyal A, Harrison SA, et al. Cenicriviroc teatment for adults with nonalcoholic steatohepatitis and fibrosis: Final analysis of the phase 2b CENTAUR study. Hepatology 2020;72:892–905.
[38] Anstee QM, Neuschwander-Tetri BA, Wai-Sun Wong V, et al. Cenicriviroc lacked efficacy to teat liver fibrosis in nonalcoholic steatohepatitis: AURORA phase III randomized study. Clin Gastroenterol Hepatol 2024;22:124–34 e121.
[39] Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679–90.
[40] Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2020;384:1113–24.
[41] Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989–1002.
[42] Wong C, Lee MH, Yaow CYL, et al. Glucagon-like peptide-1 receptor agonists for non-alcoholic fatty liver disease in type 2 diabetes: A meta-analysis. Front Endocrinol (Lausanne) 2021;12:609110.
[43] Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022;387:205–16.
[44] Urva S, Quinlan T, Landry J, et al. Effects of hepatic impairment on the pharmacokinetics of the dual GIP and GLP-1 receptor agonist tirzepatide. Clin Pharmacokinet 2022;61:1057–67.
[45] Nahra R, Wang T, Gadde KM, et al. Effects of cotadutide on metabolic and hepatic parameters in adults with overweight or obesity and type 2 diabetes: A 54-week randomized phase 2b study. Diabetes Care 2021;44:1433–42.

[46] Mantovani A, Petracca G, Csermely A, et al. Sodium-glucose cotransporter-2 inhibitors for treatment of nonalcoholic fatty liver disease: A meta-analysis of randomized controlled trials. Metabolites 2020:11.
[47] Harrison SA, Neff G, Guy CD, et al. Efficacy and safety of aldafermin, an engineered FGF19 analog, in a randomized, double-blind, placebo-controlled trial of patients with nonalcoholic steatohepatitis. Gastroenterology 2021;160:219–31 e211.
[48] Harrison SA, Ruane PJ, Freilich BL, et al. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. Nat Med 2021;27:1262–71.
[49] Harrison SA, Frias JP, Neff G, et al. Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial. Lancet Gastroenterol Hepatol 2023;8:1080–93.
[50] Loomba R, Sanyal AJ, Kowdley KV, et al. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. N Engl J Med 2023;389:998–1008.
[51] Harrison SA, Bashir MR, Guy CD, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2019;394:2012–24.
[52] Harrison SA, Taub R, Neff GW, et al. Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. Nat Med 2023;29:2919–28.
[53] 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 2024;390:497–509.
[54] European Association for the Study of the Liver; European Association for the Study of Diabetes; European Association for the Study of ObesityEASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–402.
[55] Younossi ZM, Corey KE, Lim JK. AGA clinical practice update on lifestyle modification using diet and exercise to achieve weight loss in the management of nonalcoholic fatty liver disease: Expert review. Gastroenterology 2021;160:912–18.
[56] Chitturi S, Wong VW, Chan WK, et al. The Asia-Pacific Working Party on non-alcoholic fatty liver disease guidelines 2017-Part 2: Management and special groups. J Gastroenterol Hepatol 2018;33:86–98.
[57] Societa Italiana di Diabetologia, Societa Italiana dell'ObesitaNon-alcoholic fatty liver disease in adults 2021: A clinical practice guideline of the Italian Association for the Study of the Liver (AISF), the Italian Society of Diabetology (SID) and the Italian Society of Obesity (SIO). Dig Liver Dis 2022;54:170–182.
[58] Younossi ZM, Zelber-Sagi S, Henry L, et al. Lifestyle interventions in nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 2023;20:708–22.
[59] Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51:121–9.
[60] Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149:367–78 e365quiz e314-365.
[61] Wong VW, Wong GL, Chan RS, et al. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. J Hepatol 2018;69:1349–56.
[62] Ng CH, Xiao J, Lim WH, et al. Placebo effect on progression and regression in NASH: Evidence from a meta-analysis. Hepatology 2022;75:1647–61.
[63] Marchesini G, Petta S. Dalle Grave R. Diet, weight loss, and liver health in nonalcoholic fatty liver disease: Pathophysiology, evidence, and practice. Hepatology 2016;63:2032–43.
[64] Centis E, Moscatiello S, Bugianesi E, et al. Stage of change and motivation to healthier lifestyle in non-alcoholic fatty liver disease. J Hepatol 2013;58:771–7.
[65] Ufholz K, Bhargava D. A review of telemedicine interventions for weight loss. Curr Cardiovasc Risk Rep 2021;15:17.
[66] Hsu CH, Alavi A, Dong M. Editorial: mHealth for non-communicable diseases. Front Public Health 2022;10:918982.
[67] Petroni ML, Brodosi L, Armandi A, et al. Lifestyle intervention in NAFLD: Long-term diabetes incidence in subjects treated by web- and group-based programs. Nutrients 2023;15:792–807.
[68] Petroni ML, Colosimo S, Brodosi L, et al. Long-term follow-up of web-based and group-based behavioural intervention in NAFLD in a real world clinical setting. Aliment Pharmacol Ther 2023;59:249–59.
[69] Lee Y, Doumouras AG, Yu J, et al. Complete resolution of nonalcoholic fatty liver disease after bariatric surgery: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17:1040–60 e1011.
[70] Zhou H, Luo P, Li P, et al. Bariatric surgery improves nonalcoholic fatty liver disease: Systematic review and meta-analysis. Obes Surg 2022;32:1872–83.
[71] McCarty TR, Echouffo-Tcheugui JB, Lange A, et al. Impact of bariatric surgery on outcomes of patients with nonalcoholic fatty liver disease: a nationwide inpatient sample analysis, 2004-2012. Surg Obes Relat Dis 2018;14:74–80.
[72] Bergmann NC, Davies MJ, Lingvay I, et al. Semaglutide for the treatment of overweight and obesity: A review. Diabetes Obes Metab 2023;25:18–35.
[73] Kosiborod MN, Verma S, Borlaug BA, et al. Effects of semaglutide on symptoms, function, and quality of life in patients with heart failure with preserved ejection fraction and obesity: A prespecified analysis of the STEP-HFpEF trial. Circulation 2024;149:204–16.
[74] Enebo LB, Berthelsen KK, Kankam M, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2.4 mg for weight management: a randomised, controlled, phase 1b trial. Lancet 2021;397:1736–48.
[75] Jastreboff AM, Kaplan LM, Frias JP, et al. Triple-hormone-receptor agonist retatrutide for obesity - A phase 2 trial. N Engl J Med 2023;389:514–26.
[76] Brodosi L, Petroni ML, Marchesini G. Looking ahead to potential incretin combination therapies for nonalcoholic steatohepatitis in patients with diabetes. Expert Opin Pharmacother 2023;24:989–1000.
[77] Wharton S, Blevins T, Connery L, et al. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. N Engl J Med 2023;389:877–88.
[78] Gupta U, Verma M. Placebo in clinical trials. Perspect Clin Res 2013;4:49–52.
[79] Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 2023;389:2221–32.
[80] Lazarus JV, Mark HE, Allen AM, et al. A global research priority agenda to advance public health responses to fatty liver disease. J Hepatol 2023;79:618–34.
[81] Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: The STEP 3 randomized clinical trial. JAMA 2021;325:1403–13.
[82] Petroni ML, Montesi L, Colosimo S, et al. Combination of GLP-1 receptor agonists and behavioural treatment in type 2 diabetes elicits synergistic effects on body weight: A retrospective cohort study. Endocrinol Diab Metab 2019;2:e00082.
[83] Kim Y. Emerging treatment options for sarcopenia in chronic liver disease. Life (Basel) 2021;11.
[84] Bonekamp NE, Visseren FLJ, Cramer MJ, et al. Long-term lifestyle change and risk of mortality and Type 2 diabetes in patients with cardiovascular disease. Eur J Prev Cardiol 2024;31:205–13.
[85] Khan TA, Field D, Chen V, et al. Combination of multiple low-risk lifestyle behaviors and incident type 2 diabetes: A systematic review and dose-response meta-analysis of prospective cohort studies. Diabetes Care 2023;46:643–56.
[86] Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: The STEP 4 randomized clinical trial. JAMA 2021;325:1414–25.
[87] Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med 2024;390:1394–407.