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Comparison of pharmacological therapies in metabolic dysfunction–associated steatohepatitis for fibrosis regression and MASH resolution: Systematic review and network meta-analysis

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Abstract

Background and Aims: Metabolic dysfunction–associated steatohepatitis (MASH) is a leading cause of liver disease. With the advent of multiple therapeutic targets in late-phase clinical drug development for MASH, there is a knowledge gap to better understand the comparative efficacy of various pharmacological agents. We conducted an updated network meta-analysis to evaluate the relative rank order of the different pharmacological agents for both fibrosis regression and MASH resolution.

Approach and Results: We searched PubMed and Embase databases from January 1, 2020 to December 1, 2024, for published randomized controlled trials comparing pharmacological interventions in patients with biopsy-proven MASH. The co-primary endpoints were fibrosis improvement ≥ 1 stage without MASH worsening and MASH resolution without worsening fibrosis. We conducted surface under the cumulative ranking curve (SUCRA) analysis. A total of 29 randomized controlled trials (n = 9324) were included. Pegozafermin, cilofexor + firsocostat, denifanstat, survodutide, obeticholic acid, tirzepatide, resmetirom, and semaglutide were significantly better than placebo in achieving fibrosis regression without worsening MASH. Pegozafermin (SUCRA: 79.92), cilofexor + firsocostat (SUCRA: 71.38), and cilofexor + selonsertib (SUCRA: 69.11) were ranked the most effective interventions. Pegozafermin, survodutide, tirzepatide, efruxifermin, liraglutide, vitamin E + pioglitazone, resmetirom, semaglutide, pioglitazone, denifanstat, semaglutide, and lanifibranor were significantly better than placebo in achieving MASH resolution without worsening

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CINeMA, Confidence in Network Meta-Analysis; CrI, credible interval; FDA, Food and Drug Administration; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; RCT, randomized controlled trial; RoB 2, Risk of Bias 2; SUCRA, surface under the cumulative ranking curve.

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fibrosis. Pegozafermin (SUCRA: 91.75), survodutide (SUCRA: 90.87), and tirzepatide (SUCRA: 84.70) were ranked the most effective interventions for achieving MASH resolution without worsening fibrosis.

Conclusions: This study provides updated rank-order efficacy of MASH pharmacological therapies for fibrosis regression and MASH resolution. These data are helpful to inform practice and clinical trial design.

Keywords: drugs, metabolic dysfunction–associated steatohepatitis, NASH, network meta-analysis

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD) is a leading cause of chronic liver disease, closely associated with the global epidemics of obesity and diabetes.[1–3] MASLD is an umbrella term that includes hepatic steatosis, and its inflammatory form, termed metabolic dysfunction–associated steatohepatitis (MASH), which can progress to fibrosis, cirrhosis, and HCC.[4,5] The unmet need to treat MASH and its associated comorbidities has driven drug development efforts worldwide.[6] A turning point in this journey was the recent conditional approval of resmetirom by the Food and Drug Administration (FDA) for the treatment of MASH in those with moderate to advanced fibrosis without cirrhosis.[7,8]

Newer therapies are being developed that target different mechanistic pathways to address the unmet need for greater improvements in fibrosis and MASH resolution beyond what is currently achieved with resmetirom alone.[7] Several recent randomized controlled trials (RCTs) of drugs in phase IIB have displayed positive results in achieving the histologic endpoints proposed by the FDA.[9–13] Improvements in liver histology using paired biopsy have been used as a surrogate indicator of clinical benefit for liver-related outcomes in the regulatory process for accelerated drug approval, pending further long-term validation.[14] With multiple exciting new results from recent trials, there is an unmet need to understand the efficacy of different pharmacological agents for treating MASH. These data will also help determine potential future combination therapeutic approaches in MASH to further improve treatment response rates. Therefore, we performed a systematic review and network meta-analysis to determine and rank the efficacy of pharmacological therapies for improving histologic outcomes in MASH.

METHODS

Data source and search strategy

We have preregistered a study protocol in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42024557351). This systematic review and network meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Supplemental Table S1, http://links.lww.com/HEP/J721).[15,16] We systematically searched the PubMed and Embase databases from January 1, 2020 (based on our previous systematic review by Majzoub et al[17]) to December 1, 2024. The full search strategies are provided in the Supplemental Methods, http://links.lww.com/HEP/J721. All references were imported into Rayyan for duplicate removal and further selection. We also performed a technique of backward snowballing, searching for additional studies in the reference lists of previous primary articles and relevant reviews.

Eligibility criteria

Two investigators (Matheus Souza and Lubna Al-Sharif) independently made an initial selection based on titles/abstracts, followed by a detailed full-text assessment of potentially relevant studies. Disagreements were resolved by consensus between the authors and in consultation with a third investigator (Daniel Q. Huang). The prespecified inclusion criteria were as follows: (i) RCTs by study design (phases 2–4); (ii) enrolled patients with biopsy-proven MASH; (iii) compared at least 1 established or potentially beneficial therapy for MASH based on the American Association for the Study of Liver Diseases (AASLD) guidelines[18] to each other or placebo; (iv) follow-up $\geq$6 months; and (v) reported at least 1 endpoint of interest: $\geq$1 stage improvement in fibrosis without MASH worsening; and resolution of MASH without fibrosis worsening. Studies were excluded if they were: (i) observational studies other than RCTs or non-original publications (eg, reviews, commentaries, editorials, practice guidelines); (ii) trials of lifestyle modification interventions; (iii) trials with short follow-up ($<$6 months); (iv) trials of futile therapy based on AASLD guidelines (eg, metformin, omega-3 fatty acids)[18]; (v) focused on patients with MASH-related cirrhosis; or (vi) trials with $<$40 patients.

Data extraction

The following information was extracted from each study independently by 2 investigators (Matheus Souza and Lubna Al-Sharif) and recorded in a standardized format: (i) study characteristics: first author, year of publication, geographical location, trial phase, and duration; (ii) population characteristics: number of participants, age, sex, body mass index, presence of diabetes, MASH characteristics (NAFLD Activity Score, presence and stage of fibrosis), alanine aminotransferase, and AST; (iii) treatment characteristics: dose and schedule of intervention and concomitant nonpharmacological interventions; and (iv) endpoints of interest.

Quality assessment

Two investigators (Matheus Souza and Lubna Al-Sharif) independently assessed the risk of bias for each eligible RCT, and disagreements were resolved by consensus. We used the Cochrane Risk of Bias 2 tool (RoB 2), which evaluates studies based on their random sequence generation, allocation concealment, blinding of participants and personnel, blinding of endpoint assessment, incomplete endpoint data, selective endpoint reporting, and other sources of bias.[19] Each domain was rated as low risk, with some concerns or high risk of bias.

Data synthesis and analysis

The co-primary endpoints were fibrosis improvement ≥ 1 stage without MASH worsening, and MASH resolution without fibrosis worsening. Data from eligible studies were extracted as intention-to-treat (ITT) analyses. We performed pairwise and network meta-analyses to evaluate these endpoints. First, we performed a pairwise meta-analysis to estimate the direct effect of each treatment by calculating pooled risk ratios (RRs) and 95% CIs using a random-effects model.[20] Statistical heterogeneity was assessed through I^2 and Cochran Q test values, with I^2 values around 25%, ~50%, and ~75% indicating low, moderate, and high heterogeneity, respectively. Second, we performed a Bayesian network meta-analysis with Markov Chain Monte Carlo simulation using vague priors.[21] We used generalized linear models with 4 chains, 1000 burn-ins, 10,000 iterations, and 1000 adaptations.[21] Model fit was assessed by visual inspection of the trace and density plots. Deviance information criterion and the unrelated mean effects model were used to examine consistency and further validate the transitivity assumption.[21]

Network plots were generated for each endpoint to visualize the geometry and connectivity of the evidence. Ranking of interventions for both endpoints was done with surface under the cumulative ranking (SUCRA) curve analysis.[22] The SUCRA statistic ranges from 0% to 100%, with higher values indicating better rankings for the competing intervention. The outputs of the network analysis were presented as RRs with corresponding credible intervals (CrI). To assess the robustness of our findings, we performed 3 sensitivity analyses. First, we excluded trials with a high risk of bias according to RoB 2. Subsequently, we performed sensitivity analyses based on trial duration, excluding trials with a duration of < 52 weeks and those with ≥ 52 weeks. A p value of < 0.05 was considered statistically significant. All analyses were performed using R software (version 4.2.3; gemtc, RJAGS, BUGSnet, and meta-packages). The certainty of the evidence for all estimates was determined according to the Confidence in Network Meta-Analysis (CINeMA) framework endorsed by the Cochrane Collaboration.[23,24]

RESULTS

Characteristics of the included studies

The systematic search identified 6743 potential articles. A total of 48 underwent full-text review after title/abstract screening. In addition, we included 1 abstract[25] published at a meeting with a widely disseminated protocol.[26] Sixteen new studies met the criteria for inclusion. Finally, 31 studies were included in the systematic review and network meta-analysis, reporting data from 29 RCTs (n = 9324) of biopsy-proven MASH (Figure 1).[7,9–12,25,27–51]

The main characteristics of the 29 RCTs are summarized in Supplemental Table S2, http://links.lww.com/HEP/J721. Of these, 9 trials were conducted in North America, 3 in Asia, 1 in Europe, and 16 trials were multinational. Most trials were multicenter (93.1%, 27/29). The duration of the included RCTs ranged from 24 to 72 weeks. All RCTs were placebo-controlled, except for the TANDEM trial.[49] Importantly, the ESSENCE trial has not yet been published.[25] The baseline characteristics of the participants included in the RCTs are summarized in Supplemental Table S3, http://links.lww.com/HEP/J721. Supplemental Figure S1, http://links.lww.com/HEP/J721, summarizes the risk of bias assessment for the included studies.

Fibrosis improvement ≥ 1 stage without worsening MASH

Twenty-four RCTs reported data from 8708 participants for this endpoint. Figure 2A shows the network plot for the primary endpoint, including a total of 26 interventions (aldafermin, apararenone, aramchol, cenicriviroc,

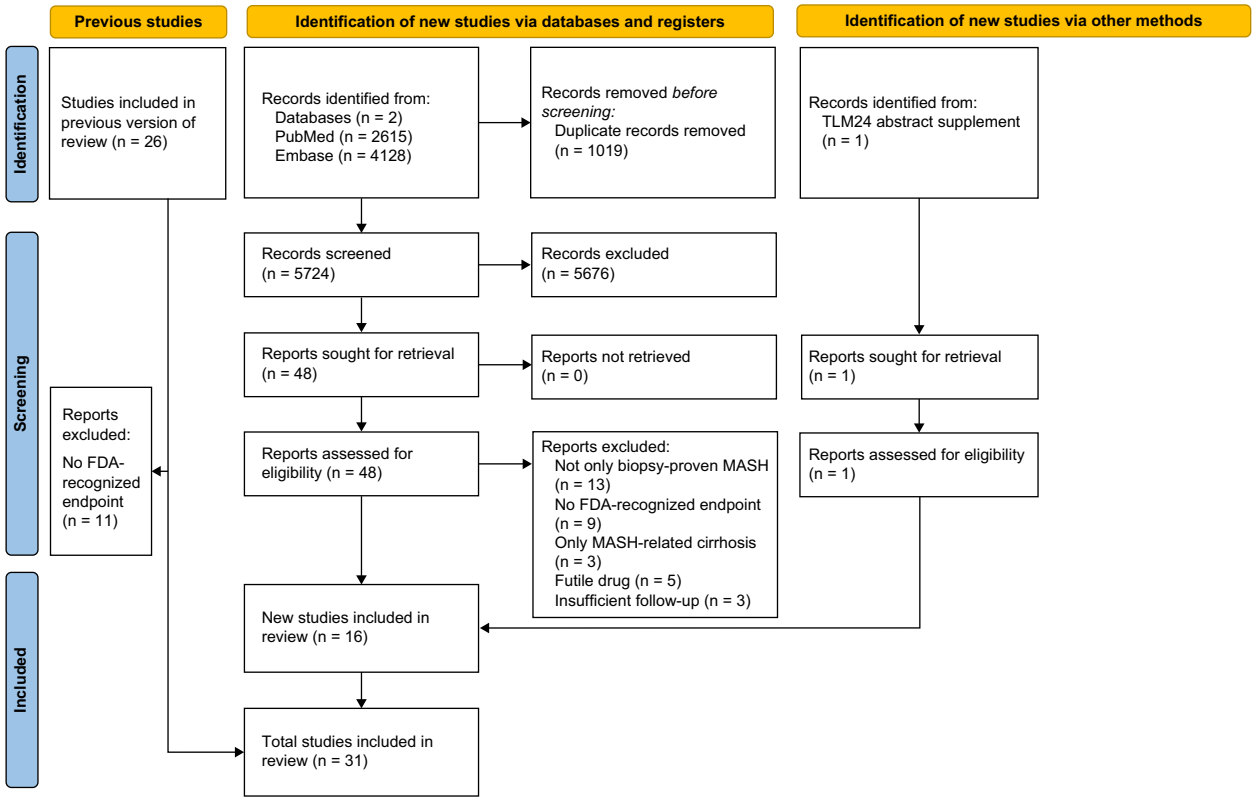

FIGURE 1 PRISMA flowchart of study screening and selection. Abbreviations: FDA, Food and Drug Administration; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

cilofexor, cilofexor + firsocostat, cilofexor + selonsertib, denifanstat, efruxifermin, firsocostat, firsocostat + selonsertib, lanifibranor, MSDC 0602K, obeticholic acid, PXL065, pegbelfermin, pegozafermin, resmetirom, selonsertib, semaglutide, survodutide, tirzepatide, tropifexor, tropifexor + cenicriviroc, vitamin E, vitamin E + pioglitazone).

Pegozafermin (RR: 3.46, CrI: 1.54–11.15), cilofexor + firsocostat (RR: 2.67, CrI: 1.05–8.13), denifanstat (RR: 1.94, CrI: 1.04–4.04), survodutide (RR: 1.86, CrI: 1.18– 3.28), obeticholic acid (RR: 1.85, CrI: 1.30–2.75), tirzepatide (RR: 1.77, CrI: 1.17–2.94), resmetirom (RR: 1.64, CrI: 1.27–2.20), and semaglutide (RR: 1.51, CrI: 1.23–1.90) were statistically better than placebo in achieving ≥ 1 stage of fibrosis improvement without worsening MASH (Figure 3A). The results of the network meta-analysis are summarized in Supplemental Figure S2A, http://links.lww.com/HEP/J721. Overall, pegozafermin ranked highest (SUCRA: 79.92) for fibrosis improvement without worsening MASH, followed by cilofexor + firsocostat (SUCRA: 71.38) and cilofexor + selonsertib (SUCRA: 69.11), while selonsertib ranked lowest (SUCRA: 11.38) (Table 1A; Supplemental Figure S3A, http://links.lww.com/HEP/J721). Pairwise comparisons among therapies are shown in Supplemental Figure S4A, http://links.lww.com/HEP/J721. Based on the CINeMA framework, the confidence in estimates for comparisons across the network is detailed in Supplemental Table S5A, http://links.lww.com/HEP/J721.

MASH resolution without worsening fibrosis

Twenty-eight RCTs reported data from 9277 participants for this endpoint. Figure 2B shows the network plot for this endpoint, including a total of 29 interventions (aldafermin, aramchol, cenicriviroc, cilofexor, cilofexor + firsocostat, cilofexor + selonsertib, denifanstat, efruxifermin, elafibranor, firsocostat, firsocostat + selonsertib, lanifibranor, liraglutide, MSDC 0602K, obeticholic acid, PXL065, pegbelfermin, pegozafermin, pioglitazone, resmetirom, selonsertib, semaglutide, silymarin, survodutide, tirzepatide, tropifexor, tropifexor + cenicriviroc, vitamin E, and vitamin E + pioglitazone).

Pegozafermin (RR: 8.65, CrI: 2.63–59.42), survodutide (RR: 6.62, CrI: 3.13–17.97), tirzepatide (RR: 4.65, CrI: 2.31–10.66), efruxifermin (RR: 3.51, CrI: 1.83–8.17), liraglutide (RR: 3.23, CrI: 1.11–14.17), vitamin E + pioglitazone (RR: 3.03, CrI: 1.31–9.04), resmetirom (RR: 2.54, CrI: 1.86–3.55), pioglitazone (RR: 2.29, CrI: 1.41–4.03), denifanstat (RR: 2.03, CrI: 1.04–4.72), semaglutide (RR: 1.87, CrI: 1.60–2.24), and lanifibranor (RR: 1.93, CrI: 1.30–3.02) were statistically better than placebo in achieving MASH resolution

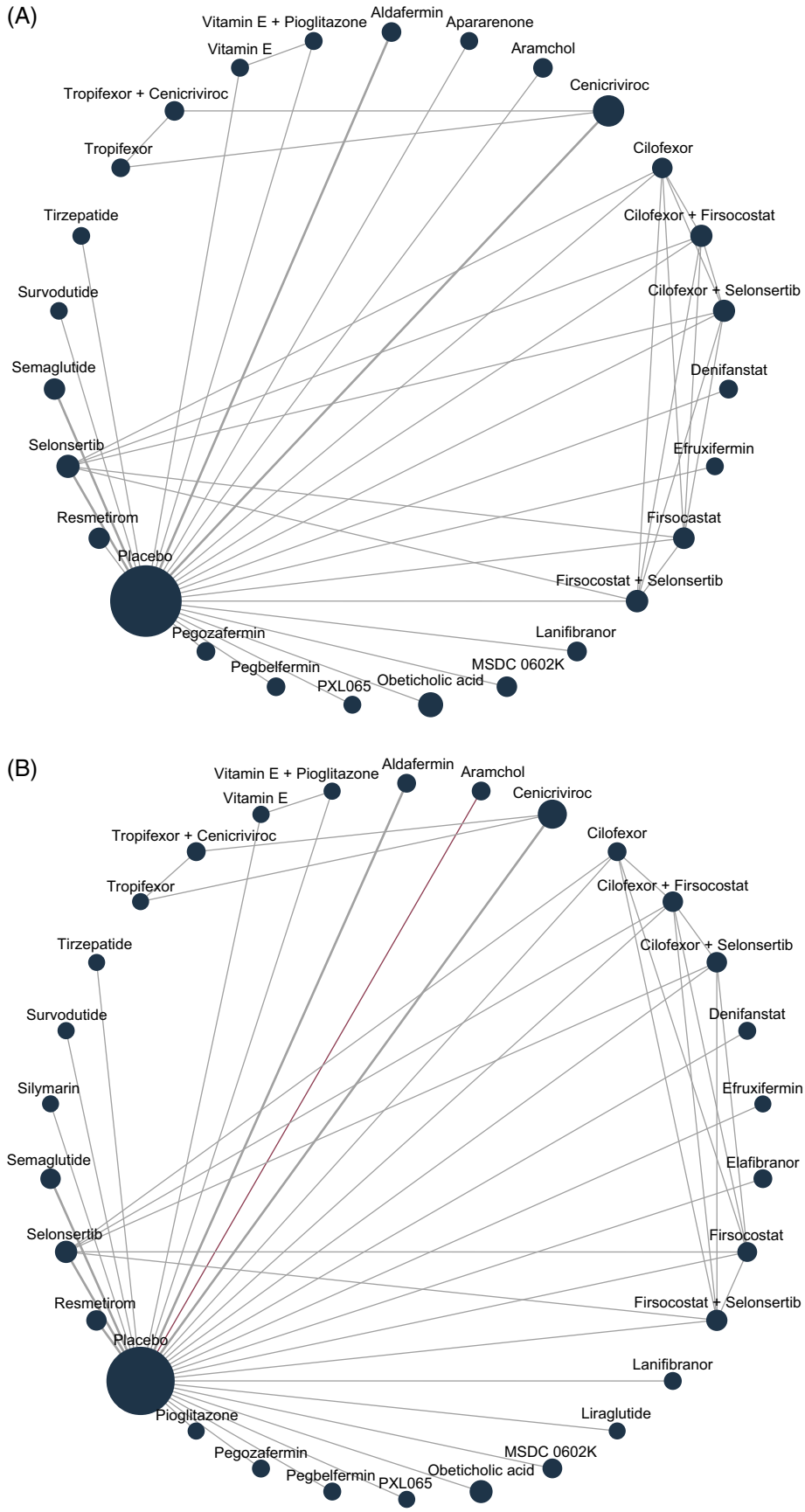

FIGURE 2 Network plots of included studies with available direct comparisons for (A) fibrosis improvement ≥ 1 stage without worsening MASH and (B) MASH resolution without worsening fibrosis endpoints. The size of the nodes correlates with the number of patients assigned, and the thickness of the edges correlates with the number of direct comparisons. Abbreviation: MASH, metabolic dysfunction–associated steatohepatitis.

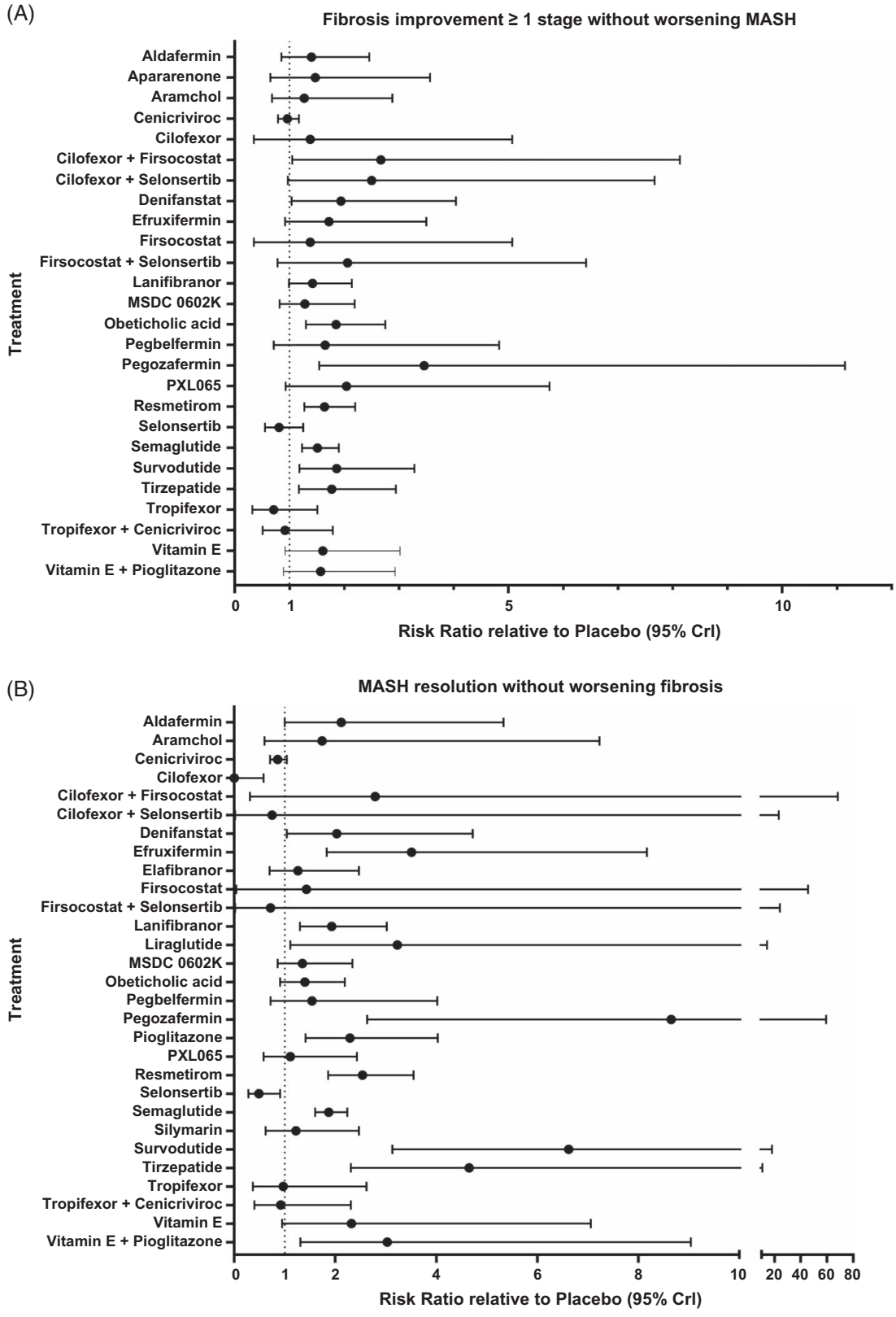

FIGURE 3 Treatment effects for (A) fibrosis improvement ≥1 stage without worsening MASH and (B) MASH resolution without worsening fibrosis endpoints. Abbreviation: MASH, metabolic dysfunction–associated steatohepatitis.

TABLE 1A SUCRA ranking of treatment for fibrosis improvement ≥1 stage without worsening MASH endpoint

Treatment	SUCRA
Pegozafermin	79.92
Cilofexor + firsocostat	71.38
Cilofexor + selonsertib	69.11
PXL065	63.27
Firsocostat + selonsertib	61.12
Denifanstat	60.64
Survodutide	59.89
Obeticholic acid	58.86
Tirzepatide	57.37
Efruxifermin	56.20
Pegbelfermin	52.13
Vitamin E	51.65
Vitamin E + pioglitazone	50.43
Resmetirom	50.14
Apararenone	47.29
Semaglutide	47.04
Lanifibranor	46.56
Aldafermin	46.35
Firsocostat	45.32
Cilofexor	44.34
Aramchol	44.27
MSDC 0602K	43.40
Tropifexor + cenicriviroc	38.32
Cenicriviroc	36.97
Tropifexor	29.26
Placebo	27.32
Selonsertib	11.38

Abbreviations: MASH, metabolic dysfunction–associated steatohepatitis; SUCRA, surface under the cumulative ranking curve.

TABLE 1B SUCRA ranking of treatment for MASH resolution without worsening fibrosis endpoint

Treatment	SUCRA
Pegozafermin	91.75
Survodutide	90.87
Tirzepatide	84.70
Efruxifermin	76.22
Liraglutide	71.58
Vitamin E + pioglitazone	71.42
Cilofexor + firsocostat	67.23
Resmetirom	63.95
Pioglitazone	62.62
Vitamin E	60.35
Aldafermin	59.91
Denifanstat	58.43
Semaglutide	57.00
Lanifibranor	55.72
Aramchol	52.13
Firsocostat	50.02
Pegbelfermin	45.82
Obeticholic acid	41.03
MSDC 0602K	40.57
Elafibrinor	38.25
Silymarin	36.47
Cilofexor + selonsertib	34.58
PXL065	33.46
Firsocostat + selonsertib	33.03
Tropifexor	31.10
Tropifexor + cenicriviroc	29.20
Placebo	25.61
Cenicriviroc	22.89
Selonsertib	10.06
Cilofexor	4.46

Abbreviations: MASH, metabolic dysfunction–associated steatohepatitis; SUCRA, surface under the cumulative ranking curve.

without worsening fibrosis. By contrast, selonsertib (RR: 0.49, CrI: 0.28–0.91) and cilofexor (RR: 0.00, CrI: 0.00–0.58) were inferior to placebo (Figure 3B). The results of the network meta-analysis are summarized in Supplemental Figure S2B, http://links.lww.com/HEP/J721. Overall, pegozafermin ranked highest (SUCRA: 91.75) for MASH resolution without worsening fibrosis, followed by survodutide (SUCRA: 90.87) and tizerpatide (SUCRA: 84.70), while cilofexor ranked lowest (SUCRA: 4.46) (Table 1B; Supplemental Figure S3B, http://links.lww.com/HEP/J721). Pairwise comparisons among therapies are shown in Supplemental Figure S4B, http://links.lww.com/HEP/J721. Based on the CINeMA framework, the confidence in estimates for comparisons across the network is detailed in Supplemental Tables S4A and S4B, http://links.lww.com/HEP/J721. Figure 4 shows a 2-dimensional plot of SUCRAs probabilities for co-primary endpoints.

Sensitivity analyses

After excluding trials with a high risk of bias, the results remained consistent (Supplemental Tables S5A and S4B, http://links.lww.com/HEP/J721). Among trials of ≥52 weeks duration, denifanstat (SUCRA: 66.49) ranked highest for fibrosis improvement without worsening MASH, followed by obeticholic acid (SUCRA: 65.90), and tirzepatide (SUCRA: 62.98) (Supplemental Table S5A, http://links.lww.com/HEP/J721). Among trials of <52 weeks duration, pegozafermin (SUCRA: 65.92) ranked highest for fibrosis improvement without worsening MASH, followed by cilofexor + firsocostat (SUCRA: 64.60), and cilofexor + selonsertib (SUCRA: 63.01) (Supplemental

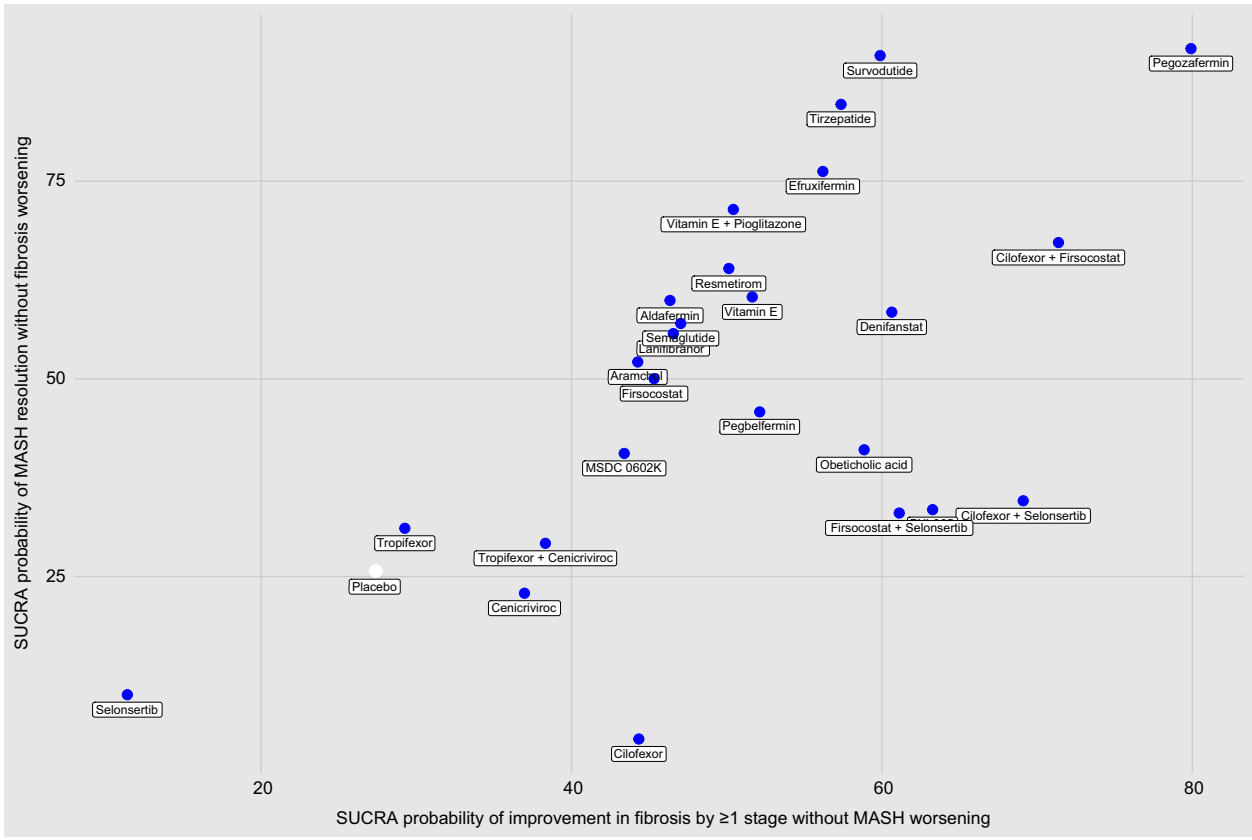

FIGURE 4 SUCRAs for the co-primary endpoints. Abbreviation: SUCRA, Surface Under the Cumulative RAnking curve.

Table S5A, http://links.lww.com/HEP/J721). Among trials of ≥52 weeks duration, tirzepatide (SUCRA: 87.03) ranked highest for MASH resolution without worsening fibrosis, followed by vitamin E + pioglitazone (SUCRA: 71.71), and resmetirom (SUCRA: 71.21) (Supplemental Table S5B, http://links.lww.com/HEP/J721). Among trials of <52 weeks duration, pegozafermin (SUCRA: 84.09) ranked highest for MASH resolution without worsening fibrosis, followed by survodutide (SUCRA: 80.68) and efruxifermin (SUCRA: 69.58) (Supplemental Table S5B, http://links.lww.com/HEP/J721).

DISCUSSION

Main findings

In this systematic review and network meta-analysis of 29 RCTs with 9324 participants with biopsy-proven MASH, we evaluated the rank-efficacy of different pharmacological therapies in achieving fibrosis regression without worsening MASH, or MASH resolution without worsening fibrosis. Pegozafermin, cilofexor + firsocostat, denifanstat, survodutide, obeticholic acid, tirzepatide, resmetirom, and semaglutide were significantly better than placebo in improving ≥1 fibrosis stage without worsening MASH. Pegozafermin (SUCRA: 79.92), cilofexor + firsocostat (SUCRA: 71.38), and cilofexor + selonsertib (SUCRA: 69.11) were ranked the most effective interventions for achieving fibrosis regression without worsening MASH.

For the endpoint of MASH resolution without fibrosis worsening, pegozafermin, survodutide, tirzepatide, efruxifermin, liraglutide, vitamin E + pioglitazone, resmetirom, semaglutide, pioglitazone, denifanstat, semaglutide, and lanifibranor were significantly better than placebo. Pegozafermin (SUCRA: 91.75), survodutide (SUCRA: 90.87), and tirzepatide (SUCRA: 84.70) were ranked the most effective interventions for achieving MASH resolution without worsening fibrosis.

In context with current literature

This network meta-analysis builds on previous meta-analyses[17,52] and provides updated estimates of the comparative efficacy of studied therapies for MASH by including new data from RCTs.[7,9–12,49] In contrast to the previous study by Majzoub et al,[17] we included only studies that utilize the endpoints currently accepted by the FDA for drug approval[14] and we used intention-to-treat analysis, considering the worst-case scenario (ie, each dropout as a treatment failure) for a conservative interpretation of the results.

In particular, the results of this network meta-analysis suggest that FGF21 analogs (such as pegozafermin) and

glucagon and GLP-1 receptor agonists (such as survodutide and tirzepatide) may improve fibrosis and resolve MASH. However, the available evidence indicates that larger trials are needed to validate these findings before clinical use in MASH. Our data also support the efficacy of the recently approved resmetirom and provide relative efficacy of other drugs in the pipeline.

Strengths and limitations

The current study provides updated relative-ranked data on the histologic efficacy of existing and novel MASH therapeutic agents. However, this study has several limitations. First, we acknowledge the modest number of trials with direct comparisons between pharmacological therapies, and the small number of trials for each agent; hence, most comparisons between treatments were based on indirect evidence; head-to-head trials versus other drugs should be considered to validate our findings. Many of the earlier phase trials included in this study had a small number of participants distributed across different doses in each arm. Comparability between trials was further limited by their heterogeneity in design and population (eg, demographics and comorbidities).[53] Some of the therapeutic agents included in this study, such as obeticholic acid, are no longer being developed for MASH. The inclusion of therapeutic agents in earlier phases requires cautious interpretation, as many of these agents may never achieve FDA approval related to safety or efficacy issues. The trials were performed across different populations and for varying durations, hence cautious interpretation is required, although we performed a sensitivity analysis for the duration of the trials. The therapeutic agents included in this study have varying extrahepatic effects; hence, in the future, when multiple approved therapies are available for MASH, it is likely that the choice of therapy will depend on the presence of comorbidities rather than modest differences in efficacy related to MASH resolution or fibrosis regression. Liver biopsy is the gold standard for endpoint assessment; however, there are concerns about the accuracy and consistency of manual histology assessments, hence the need for better noninvasive tests.[54,55] Finally, we were unable to assess evidence of publication bias due to the small number of trials included in each comparison.

Implications for future research and clinical practice

These data have important implications for trial design. We contextualize our data within the AASLD guidelines and provide a framework for recommendations and future updates. As novel therapies are on the horizon, these data highlight the potential of these emerging therapies and add the comparative notion of their efficacy based on histologic improvements. Our study also provides insight into potential combinations of therapies to enhance histological results in future trials.

In conclusion, this network meta-analysis provides contemporaneous and relative rank-order evidence on the efficacy of MASH therapies for achieving fibrosis regression and MASH resolution. These data may help the development of combination therapies, which are likely to improve histologic response with further treatment of comorbidities. These data inform the design of future clinical trials and warrant prospective validation in head-to-head trials.

DATA AVAILABILITY STATEMENT

All articles in this manuscript are available from PubMed and Embase.

AUTHOR CONTRIBUTIONS

Conceptualization: all authors; formal analysis: all authors; funding acquisition: Daniel Q. Huang, Rohit Loomba; methodology: all authors; supervision: Rohit Loomba; writing – original draft: Matheus Souza; writing – review & editing: all authors.

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CONFLICTS OF INTEREST

Daniel Q. Huang consults for, advises, and is on the speakers' bureau for Roche. He consults for and advises Gilead. Rohit Loomba consults for and received grants from Arrowhead, AstraZeneca, Eli Lilly, Gilead, Intercept, Inventiva, Ionis, Janssen, Madrigal, Merck, Novo Nordisk, Pfizer, and Terns. He consults for Aardvark, Altimmune, Cascade, Glympse Bio, Inipharma, Lipidio, Neurobo, Sagimet, 89 Bio, Takeda, and Viking. He received grants from Boehringer-Ingelheim, Bristol-Myers Squibb, Galectin, Hanmi, and Sonic Incytes. He has stock options in Sagimet Biosciences and is a co-founder of LipoNexus Inc. The remaining authors have no conflicts to report.

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REFERENCES

1. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): A systematic review. Hepatology. 2023;77:1335–47.
2. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology. 2023;78:1966–86.
3. Huang DQ, Noureddin N, Ajmera V, Amangurbanova M, Bettencourt R, Truong E, et al. Type 2 diabetes, hepatic decompensation, and hepatocellular carcinoma in patients with non-alcoholic fatty liver disease: An individual participant-level data meta-analysis. Lancet Gastroenterol Hepatol. 2023;8:829–36.
4. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: Trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2021;18:223–38.
5. Huang DQ, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E, et al. Global epidemiology of cirrhosis—Aetiology, trends and predictions. Nat Rev Gastroenterol Hepatol. 2023;20:388–98.
6. Harrison SA, Loomba R, Dubourg J, Ratziu V, Noureddin M. Clinical trial landscape in NASH. Clin Gastroenterol Hepatol. 2023;21:2001–14.
7. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med. 2024;390:497–509.
8. Francque S, Krag A, Shawcross DL, Zelber-Sagi S. A turning point in hepatology? EASL reflects on the first approved drug for MASH. J Hepatol. 2024;81:192–4.
9. Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. N Engl J Med. 2024;391:299–310.
10. Sanyal AJ, Bedossa P, Fraessdorf M, Neff GW, Lawitz E, Bugianesi E, et al. A phase 2 randomized trial of survodutide in MASH and fibrosis. N Engl J Med. 2024;391:311–9.
11. Harrison SA, Frias JP, Neff G, Abrams GA, Lucas KJ, Sanchez W, 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.
12. Loomba R, Sanyal AJ, Kowdley KV, Bhatt DL, Alkhouri N, Frias JP, et al. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. N Engl J Med. 2023;389:998–1008.
13. Tincopa MA, Anstee QM, Loomba R. New and emerging treatments for metabolic dysfunction-associated steatohepatitis. Cell Metab. 2024;36:912–26.
14. Rinella ME, Tacke F, Sanyal AJ, Anstee QM. Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD. J Hepatol. 2019;71:823–33.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
16. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. Ann Intern Med. 2015;162:777–84.
17. Majzoub AM, Nayfeh T, Barnard A, Munaganuru N, Dave S, Singh S, et al. Systematic review with network meta-analysis: Comparative efficacy of pharmacologic therapies for fibrosis improvement and resolution of NASH. Aliment Pharmacol Ther. 2021;54:880–9.
18. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology. 2023;77:1797–835.
19. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
20. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. Int J Evid Based Healthc. 2015;13:196–207.
21. Béliveau A, Boyne DJ, Slater J, Brenner D, Arora P. BUGSnet: An R package to facilitate the conduct and reporting of Bayesian network meta-analyses. BMC Med Res Methodol. 2019;19:196.
22. Mbuagbaw L, Rochwerg B, Jaeschke R, Heels-Andsell D, Alhazzani W, Thabane L, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. Syst Rev. 2017;6:79.
23. Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M, Salanti G. CINeMA: Software for semiautomated assessment of the confidence in the results of network meta-analysis. Campbell Syst Rev. 2020;16:e1080.
24. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. PLoS Med. 2020;17:e1003082.
25. Newsome PN, Sanyal AJ, Kliers I, Østergaard LH, Long MT, Kjær MS, et al. Phase 3 ESSENCE trial: Semaglutide in metabolic dysfunction-associated steatohepatitis (MASH). In: The Liver Meeting: Late Breaking Abstract Supplement, American Association for the Study of Liver Diseases; 2024. Abstract #5018.
26. Newsome PN, Sanyal AJ, Engebretsen KA, Kliers I, Østergaard L, Vanni D, et al. Semaglutide 2.4 mg in participants with metabolic dysfunction-associated steatohepatitis: Baseline characteristics and design of the phase 3 ESSENCE trial. Aliment Pharmacol Ther. 2024;60:1525–33.
27. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, 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.
28. Ratziu V, Harrison SA, Francque S, Bedossa P, Lehert P, Serfaty L, et al. Elafibranor, an agonist of the peroxisome proliferator-activated receptor-α and -δ, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology. 2016;150:1147–159.e5.
29. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: A randomized trial. Ann Intern Med. 2016;165:305–15.
30. Wah Kheong C, Nik Mustapha NR, Mahadeva S. A randomized trial of silymarin for the treatment of nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol. 2017;15:1940–49.e8.
31. Friedman SL, Ratziu V, Harrison SA, Abdelmalek MF, Aithal GP, Caballeria J, et al. A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. Hepatology. 2018;67:1754–67.
32. Ratziu V, Sanyal A, Harrison SA, Wong VWS, Francque S, Goodman Z, et al. Cenicriviroc treatment for adults with

nonalcoholic steatohepatitis and fibrosis: Final analysis of the phase 2b CENTAUR study. Hepatology. 2020;72:892–905.
33. Bril F, Biernacki DM, Kalavalapalli S, Lomonaco R, Subbarayan SK, Lai J, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: A randomized controlled trial. Diabetes Care. 2019;42:1481–8.
34. Sanyal AJ, Ratziu V, Loomba R, Anstee QM, Kowdley KV, Rinella ME, et al. Results from a new efficacy and safety analysis of the REGENERATE trial of obeticholic acid for treatment of pre-cirrhotic fibrosis due to non-alcoholic steatohepatitis. J Hepatol. 2023;79:1110–20.
35. Younossi ZM, Ratziu V, Loomba R, Rinella M, Anstee QM, Goodman Z, 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.
36. Harrison SA, Bashir MR, Guy CD, Zhou R, Moylan CA, Frias JP, 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.
37. Harrison SA, Alkhouri N, Davison BA, Sanyal A, Edwards C, Colca JR, 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.
38. Harrison SA, Wong VWS, Okanoue T, Bzowej N, Vuppalanchi R, Younes Z, 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.
39. Harrison SA, Neff G, Guy CD, Bashir MR, Paredes AH, Frias JP, 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;160:219–231.e1.
40. Ratziu V, de Guevara L, Safadi R, Poordad F, Fuster F, Flores-Figueroa J, et al. Aramchol in patients with nonalcoholic steatohepatitis: A randomized, double-blind, placebo-controlled phase 2b trial. Nat Med. 2021;27:1825–35.
41. Loomba R, Noureddin M, Kowdley KV, Kohli A, Sheikh A, Neff G, et al. Combination therapies including cilofexor and firsocostat for bridging fibrosis and cirrhosis attributable to NASH. Hepatology. 2021;73:625–43.
42. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med. 2021;384:1113–24.
43. Okanoue T, Sakamoto M, Harada K, Inagaki M, Totsuka N, Hashimoto G, et al. Efficacy and safety of apararenone (MT-3995) in patients with nonalcoholic steatohepatitis: A randomized controlled study. Hepatol Res. 2021;51:943–56.
44. Huang JF, Dai CY, Huang CF, Tsai PC, Yeh ML, Hsu PY, et al. First-in-Asian double-blind randomized trial to assess the efficacy and safety of insulin sensitizer in nonalcoholic steatohepatitis patients. Hepatol Int. 2021;15:1136–47.
45. Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, et al. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. N Engl J Med. 2021;385:1547–58.
46. Harrison SA, Abdelmalek MF, Neff G, Gunn N, Guy CD, Alkhouri N, et al. Aldafermin in patients with non-alcoholic steatohepatitis (ALPINE 2/3): A randomised, double-blind, placebo-controlled, phase 2b trial. Lancet Gastroenterol Hepatol. 2022;7:603–16.
47. Harrison SA, Thang C, Bolze S, Dewitt S, Hallakou-Bozec S, Dubourg J, 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.
48. Anstee QM, Neuschwander-Tetri BA, Wai-Sun Wong V, Abdelmalek MF, Rodriguez-Araujo G, Landgren H, et al. Cenicriviroc lacked efficacy to treat liver fibrosis in nonalcoholic steatohepatitis: AURORA phase III randomized study. Clin Gastroenterol Hepatol. 2024;22:124–134.e1.
49. Anstee QM, Lucas KJ, Francque S, Abdelmalek MF, Sanyal AJ, Ratziu V, et al. Tropifexor plus cenicriviroc combination versus monotherapy in nonalcoholic steatohepatitis: Results from the phase 2b TANDEM study. Hepatology. 2023;78:1223–39.
50. Loomba R, Sanyal AJ, Nakajima A, Neuschwander-Tetri BA, Goodman ZD, Harrison SA, et al. Pegbelfermin in patients with nonalcoholic steatohepatitis and stage 3 fibrosis (FALCON 1): A randomized phase 2b study. Clin Gastroenterol Hepatol. 2024;22:102–112.e9.
51. Loomba R, Bedossa P, Grimmer K, Kemble G, Bruno Martins E, McCulloch W, et al. Denifanstat for the treatment of metabolic dysfunction-associated steatohepatitis: A multicentre, double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Gastroenterol Hepatol. 2024;9:1090–100.
52. Singh S, Khera R, Allen AM, Murad MH, Loomba R. Comparative effectiveness of pharmacological interventions for nonalcoholic steatohepatitis: A systematic review and network meta-analysis. Hepatology. 2015;62:1417–32.
53. Cipriani A, Higgins JPT, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. Ann Intern Med. 2013;159:130–7.
54. Harrison SA, Dubourg J. Liver biopsy evaluation in MASH drug development: Think thrice, act wise. J Hepatol. 2024;81:886–94.
55. Loomba R, Amangurbanova M, Bettencourt R, Madamba E, Siddiqi H, Richards L, et al. MASH Resolution Index: Development and validation of a non-invasive score to detect histological resolution of MASH. Gut. 2024;73:1343–9.

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