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Letter to the Editor

Treatment of Metabolic Dysfunction-associated Steatotic Liver Disease: High Hopes and Ongoing Challenges

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Dear Editor,

We read with great interest the review article by Nasir SA *et al*.,[1] recently published in the *Journal of Translational Gastroenterology*, which discusses innovative treatment regimens for patients with metabolic dysfunction-associated steatotic liver disease (MASLD). The prevalence of MASLD is increasing worldwide due to rising rates of obesity and type 2 diabetes mellitus, and it has currently become the leading cause of liver cirrhosis and liver transplantation in the Western world.[2] Traditionally, patients with MASLD have been treated by addressing the underlying metabolic risk factors, including efforts to reduce body weight, increase exercise frequency, and improve serum glucose and lipid levels.[3] Unfortunately, many patients struggle to sustain a healthy lifestyle over time. Additionally, the lack of specific treatments aimed at reversing liver fibrosis has contributed to the rising rates of end-stage liver disease associated with MASLD.

A significant milestone in MASLD management came in March 2024 when the Food and Drug Administration approved resmetirom (RES), a selective β1 thyroid hormone receptor blocker, for the treatment of patients with MASLD and significant or advanced (F2/F3) fibrosis. This approval followed the MAESTRO study, a phase III randomized controlled trial (RCT), in which RES demonstrated metabolic dysfunction-associated steatohepatitis (MASH) resolution without worsening fibrosis in 25.9% to 29.9% of patients (at doses of 80 mg and 100 mg, respectively), compared to 9.7% in the placebo group. Additionally, fibrosis improved by at least one stage without worsening MASH in 24.2% to 25.9% of patients, compared to 14.2% in the placebo group after a 52-week treatment period.[4] Exciting news was also recently announced by the company responsible for semaglutide (SEM), a glucagon-like peptide (GLP)-1 receptor agonist (RA). After completing part one of the ongoing ESSENCE trial, SEM displayed a 37% fibrosis improvement with no worsening of MASH in the once-weekly 2.4 mg SEM group, compared to 22.5% in the placebo group. It also showed resolution of MASH with no worsening of liver fibrosis in 62.9% of treated patients, compared to 34.1% in the placebo group (clinical trial NCT04822181). Prior to this promising data, SEM had been associated with improvement in liver steatosis, lobular inflammation, and hepatocellular ballooning, but not with fibrosis regression.[5,6] In addition to SEM, tirzepatide (TZP), a dual GLP1-RA plus gastrointestinal peptide RA, in a phase II RCT, recently demonstrated MASH reversal without worsening fibrosis in 44%, 56%, and 62% of F2/F3 patients (on doses of 5mg, 10 mg, or 15mg once weekly, respectively), compared to 10% in the placebo group. TZP also regressed fibrosis by at least one stage without worsening MASH in 55%, 51%, and 51% of patients, as the dose increased, compared to 30% in the placebo group.[7] These promising results add to the previously known beneficial effect of TZP on reducing liver fat content in patients with diabetes and MASLD, as assessed by magnetic resonance imaging proton density fat fraction.[8]

Beyond thyroid hormone analogs and GLP1-based therapies, two additional molecules—pegozafermin (PEG), a long-acting glycopegylated fibroblast growth factor 21, and denifanstat, an oral fatty acid synthase inhibitor—have shown encouraging results in phase IIb RCTs. PEG improved fibrosis in 22%, 26%, and 27% of F2/F3 patients in the 15 mg, 30 mg, and 44 mg once-weekly dose groups, respectively, compared to 7% in the placebo arm. Moreover, PEG achieved MASH resolution in 37%, 23%, and 26% of patients, depending on the dose, compared to 2% in the placebo group.[9] Regarding denifanstat, a dose of 50 mg yielded a 2-point or higher improvement in nonalcoholic fatty liver disease activity score without worsening fibrosis in 38% of participants, compared to 16% in the placebo group. Additionally, 26% of treated individuals achieved complete MASH resolution compared to 11% in the placebo group.[10] Notably, all the drugs discussed above are generally well tolerated by patients. Gastrointestinal disturbances, including nausea and diarrhea, are the most common side effects and are usually manageable. The incidence of serious adverse events or life-threatening reactions appears to be similar between these medications and placebo, making them a safe treatment option for individuals suffering from MASLD. Nonetheless, it is essential to investigate whether this favorable safety profile extends to patients with cirrhosis. The data from the studies discussed above are summarized in Table 1.

Nasir SA *et al*.[1] reported several other drugs that target different pathophysiological pathways of MASLD, including obeticholic acid (a farnesoid X receptor agonist); selonsertib (an apoptosis signal-regulating kinase 1 inhibitor); simtuzumab (a monoclonal antibody that targets lysyl oxidase-like 2); aldafermin (a fibroblast

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Table 1. Summary of the results from studies on new molecules for managing MASLD

Treatment class	Agent	MASH resolution (versus placebo)	Fibrosis regression by at least one stage without worsening of MASH (versus placebo)	Serious adverse events (versus placebo)
β1THRb (MAESTRO trial)	Resmetirom (80 or 100 mg daily)	25.9% and 29.9%, respectively, vs. 9.7%	24.2% and 25.9%, respectively, vs. 14.2%	10.9–12.7% (as the dose increased) vs. 11.5%
GLP1-RA (ESSENCE trial)	Semaglutide (2.4 mg once weekly)	62.9% vs.34.1%	37% vs.22.5%	No serious events presented
GLP1/GP-RA (SYNERGY-NASH trial)	Tirzepatide (5, 10, 15 mg once weekly)	44%, 56%, and 62% (as the dose increased) vs. 10%	55%, 51%,51% (as the dose increased) vs. 30%	No serious events presented
FGF21 (NCT04929483 trial)	Pegozafermin (15, 30, 44 mg once weekly	37%, 23%, and 26%, respectively, vs. 2%	22%, 26%, and 27% (as the dose increased) vs. 7%	5%, 4%, 11% (as the dose increased) vs. 4%
FASI (NCT04906421 trial)	Denifanstat (50 mg daily)	26% vs. 11%	Not studied	12% vs. 5% Not considered drug-related

FASI, fatty acid synthase inhibitor; FGF21, fibroblast growth factor 21; GLP1/GP-A, dual glucagon-like peptide-1 receptor agonist and gastrointestinal peptide receptor agonist; GLP1-RA, glucagon-like peptide-1 receptor agonist; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; β1THRb, β1 thyroid hormone receptor blocker.

growth factor 19 analog); emricasan (a caspase inhibitor); and belapectin (a galectin-3 inhibitor). Unfortunately, these agents did not meet the primary endpoints in phase II and III trials.[1] However, it remains to be investigated whether these negative results are due to the ineffectiveness of the drugs themselves or flaws in the studies' design. Indeed, most of the studies had short follow-up periods, which were likely inadequate for assessing the reversal of fibrosis, even if the administered drug showed potential effectiveness. At this point, it is worth highlighting that, in addition to the pharmaceutical agents reported by Nasir *et al*.,[1] a rich array of traditional Chinese herbal remedies has recently demonstrated promising outcomes in basic research and animal studies.[11] These herbal formulations appear to alleviate fat accumulation in the liver and reduce inflammation by targeting various key molecular pathways implicated in the development of MASLD. However, rigorous clinical trials and RCTs must be conducted to fully assess the potential efficacy and safety of these medicines in human populations suffering from MASLD.

Considering the current data, it appears that RES, GLP1-RA, GLP1/gastrointestinal peptide-RA, and PEG will likely become the mainstay of MASLD treatment in the near future.[12] Nonetheless, some issues remain unresolved. First, the percentage of patients who experience a reversal of fibrosis using these agents is still insufficient, ranging from 25–30% for RES and PEG to 50% for TZP. Second, the duration of studies is relatively short, lasting between 24 and 52 weeks, raising concerns about potential long-term adverse events and the sustainability of the drug's efficacy. Third, the safety and effectiveness of these medications have not been assessed in patients with MASLD and cirrhosis. While some studies are underway for this challenging population, their results are not expected to be available imminently. Finally, according to the latest American Association for the Study of Liver Diseases (AASLD) guidelines for RES therapy, liver biopsy is not required to diagnose F2 or F3 fibrosis.[13] Instead, liver stiffness measurements obtained through transient elastography (TE) or magnetic resonance elastography are recommended for this diagnosis.[13] However, magnetic resonance elastography is not widely available, and its cost is high, while the accuracy of TE in identifying significant fibrosis (≥F2) in obese patients with MASLD seems to be moderate.[14] Moreover, the optimal TE cut-off value proposed for diagnosing ≥F2 fibrosis varies across studies.[3] In addition, the evaluation of treatment responses using TE needs further validation. An early decrease in TE measurements after treatment initiation probably does not indicate an actual reversal of fibrosis but rather correlates with improvement in inflammation. TE measurements after six or twelve months might better reflect changes in liver fibrosis.[3,12]

In conclusion, significant expectations exist for managing patients diagnosed with MASLD. New pharmacological agents have either been introduced or are currently under investigation, raising hopes for successful treatment outcomes. However, key issues remain unresolved, such as determining the optimal duration of treatment, evaluating treatment responses, and managing patients who do not respond to a given therapy. Combining different therapeutic agents might be a potential strategy for these non-responsive cases. In addition to treating liver disease, every patient with MASLD should receive care from a multidisciplinary team to manage cardiometabolic and extrahepatic issues. Furthermore, it is essential to establish national, regional, and global policies to reduce the prevalence of the underlying metabolic risk factors predisposing individuals to the development of MASLD.

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Conflict of interest

DSK has been an Editorial Board Member of *Journal of Translational Gastroenterology* since 2025. The author has no other conflict of interest to declare.

Author contributions

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