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Incretin-based therapy for MASH: are two better than one?

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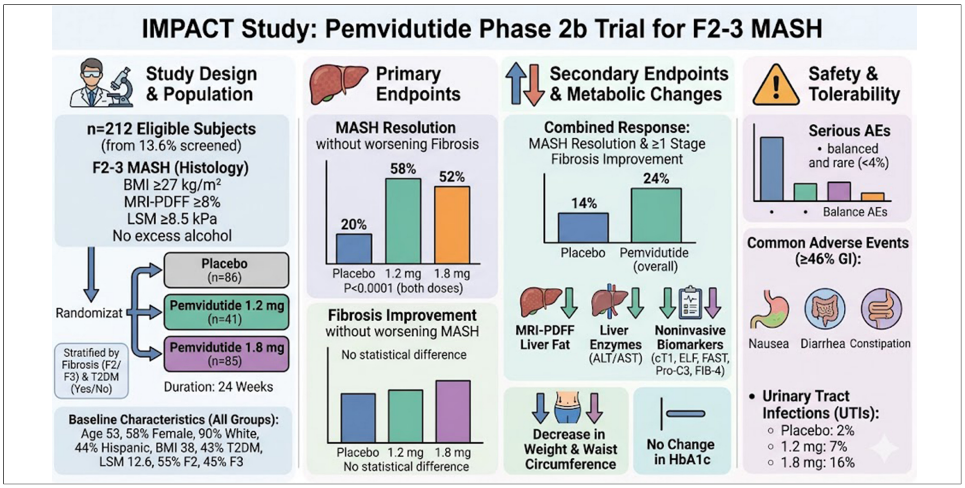

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become a global health problem affecting almost 40% of the adult population, with the highest prevalence in those with type 2 diabetes mellitus (T2DM)[1,2] and obesity[3]. MASLD can present as simple steatosis (defined as at least 5% fat in the liver), steatosis with inflammation (steatohepatitis), or steatohepatitis with hepatocyte ballooning and fibrosis (metabolic dysfunction-associated steatohepatitis, MASH). Because those with MASH are at highest risk of developing cirrhosis and liver-related outcomes [hepatic decompensation and hepatocellular carcinoma (HCC)], that has been the MASLD group targeted for therapy.

In the last few years, two therapies have been approved for MASH with stage 2-3 fibrosis (F2-3). The primary outcomes of these trials are an improvement in MASH without worsening fibrosis and improvements in fibrosis without worsening MASH. Resmetirom, approved in 2024, targets the thyroid hormone receptor beta (THR-β)[4]. In the phase 3, 240-week study, patients were randomized to resmetirom 80 mg, 100 mg, or placebo. Of the 996 enrolled subjects, steatohepatitis resolution was achieved

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in 25.9% (80 mg dose) and 29.9% (100 mg dose) compared to 9.7% in those on placebo. Fibrosis improvements were observed in 24.2% (80 mg dose) and 25.9% (100 mg dose) compared to 14.2% on placebo[5]. Incretin-based therapy for MASH can include a glucagon-like peptide 1 (GLP-1) receptor agonist (RA) alone or in dual-target combination with a glucose-dependent insulinotropic polypeptide (GIP) agonist or glucagon RA[6].

In 2025, incretin-based therapy with Semaglutide (a GLP-1 RA) was approved. In the phase 3, 72-week study, 1,197 patients with F2-3 MASH were randomized 2:1 to subcutaneous semaglutide 2.4 mg/week or placebo, with 62.9% achieving steatohepatitis resolution and 36.8% achieving reduction in fibrosis compared to 34.3% steatohepatitis resolution and 22.4% fibrosis reduction in those on placebo[7]. Dual-acting agents are another therapy option. In a phase 2 trial, tirzepatide (GLP-1 RA/GIP agonist) demonstrated 56%-62% achieving resolution of MASH and 51% achieving at least 1 stage of fibrosis compared to 10% MASH resolution and 30% fibrosis improvement in those on placebo[8]. Similarly, in a phase 2 study of survodutide (GLP-1 RA/glucagon RA) in MASH with F1-3, 62% had improvement in MASH and 34% had improvement in fibrosis compared to 14% improvement in MASH and 22% in fibrosis in the placebo group[9]. All these trials are somewhat limited by drug side effects and discontinuations.

RESEARCH SUMMARY

As opposed to the prior studies of GLP-1 RA or dual drugs that often require starting at a lower dose then increasing to the desired dose if tolerated, the pharmacokinetic properties of pemvidutide (GLP-1 RA/glucagon RA) allow starting at the target dose. In the current phase 2b study, Noureddin and colleagues studied the safety and efficacy of weekly pemvidutide in patients with F2-3 MASH (IMPACT)[10]. In this phase 2 study, 212 eligible subjects (13.6% of those screened) were randomized to 24 weeks of pemvidutide 1.2 mg (n = 41), 1.8 mg (n = 85), or placebo (n = 86) stratified by fibrosis (F2 or F3) and presence/absence of T2DM. All subjects had MASH (F2-3 by histology, a body mass index (BMI) of at least 27 kg/m^2, fat fraction by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) of at least 8%, and liver stiffness measurement (LSM) of at least 8.5 kPa without excess alcohol use. Primary end points were improvement in MASH without worsening fibrosis and improvements in fibrosis without worsening MASH. Secondary endpoints were proportion achieving both MASH resolution and fibrosis improvement, change in MRI-PDFF fat fraction, liver enzymes, and several noninvasive biomarkers [corrected T1 (cT1) relaxation, enhanced liver fibrosis (ELF) test, FibroScan-asparate aminotransferase (FAST), Pro-C3 and fibrosis-4 (FIB-4) index]. The groups were well matched: age 53 years, 58% female, 90% White, 44% Hispanic, BMI 38 kg/m^2, 43% had T2DM, LSM 12.6 kPa with 55% F2 and 45% F3.

MASH resolution without worsening of fibrosis was observed in 58% in the 1.2 mg group and 52% in the 1.8 mg group on pemvidutide compared to 20% on placebo (P < 0.0001 for both). There were no differences in improvement in fibrosis without worsening of MASH among the groups (28%-36%). Among secondary endpoints, 24% had MASH resolution combined with at least 1 stage in fibrosis on pemvidutide compared to 14% with placebo. Those on pemvidutide also had improvements in fat fraction, liver enzymes, and noninvasive biomarkers. They also had a decrease in weight and waist circumference but not glycated hemoglobin (HbA1c). Any adverse events were common across the groups but serious events were rare (< 4%) and similar across groups. Common adverse events were gastrointestinal (nausea, diarrhea, constipation) in 46% and urinary tract infections (7% in the 1.2 mg group and 16% in the 1.8 mg group compared to 2% in the placebo group).

LIMITATIONS AND CONCLUSIONS

The mainstay for management of all patients with MASLD includes minimizing alcohol use, healthy lifestyle including weight loss through diet and exercise, and identification of cardiovascular and kidney disease. This

Table 1. Comparing incretin-based therapies in MASH

Study author[Ref.]	Therapy	Target	Duration (weeks)	MASH resolution without worsening fibrosis	Fibrosis improvement without worsening MASH
Harrison *et al.*[5]	Resmetirom	THR-β RA	52	25.9%-29.9%[a]	24.2%-25.9%
Sanyal *et al.*[7]	Semaglutide	GLP-1 RA	240	62.9%	36.8%
Loomba *et al.*[8]	Tirzepatide	GLP-1 RA/GIP RA	52	44%-62%[b]	51%-55%
Sanyal *et al.*[9]	Survodutide	GLP-1 RA/Glucagon RA	48	42%-62%[c]	34%-36%
Noureddin *et al.*[10]	Pemvidutide	GLP-1 RA/Glucagon RA	24	52%-58%[d]	28%-36%

Ranges for [a]80 and 100 mg/day doses; [b]5, 10, and 15 mg/day doses; [c]2.4, 4.8, and 6.0 mg/day doses; [d]1.2 and 1.8 mg/day doses. THR-β: Thyroid hormone receptor beta; GLP-1: glucagon-like peptide 1; GIP: glucose-dependent insulinotropic polypeptide 1; RA: receptor agonist.

often requires a multidisciplinary team. In those with MASH, identified through noninvasive tests (FIB-4, elastography, ELF, or other "at risk MASH" model), treatments can be considered. Those with cirrhosis will need HCC surveillance and screening for esophageal varices in those at risk. Incretin-based therapies for MASH seem to provide greater resolution of MASH without worsening of fibrosis compared to THR-β directed treatment.

However, there are several important differences across the trials and cross-trial comparison should be interpreted with caution due to differences in study design, treatment duration, and patient populations limiting comparisons [Table 1]. In the current trial, while the primary end point of MASH improvement was met, patients on pemvidutide did not have improved fibrosis compared to placebo. This may have been due to the shorter duration of treatment (24 weeks) compared to other studies with longer duration (52-72 weeks), engagement of differential pathways, or sampling error associated with liver biopsy. However, because the study showed decreases in several noninvasive biomarkers, future studies of longer duration will be able to address that limitation. Because obesity is common in those with MASLD, weight loss is an important secondary benefit of incretin therapies that may not occur in those on THR-β directed treatment. In this trial, moderate weight loss was seen. For other GLP-1 RA treatments that also have use in primary treatments of T2DM, use of pemvidutide did not have a significant change in HbA1c compared to placebo. This may be due to the relative proportion of GLP-1 RA compared to the other drug (glucagon RA in this case). If this holds true in a larger phase 3 study, it may impact its use in those with T2DM. Notwithstanding these limitations, the study supports the need for a phase 3 trial of longer duration to determine if pemvidutide should be in the growing armamentarium in the treatment of MASH. Mechanistically, dual-target therapy, like pemvidutide may be better than GLP-1 RA monotherapy by targeting enhanced fatty acid oxidation, inhibition of lipogenesis, increased energy expenditure, and hepatic lipid mobilization in addition to the indirect effects on inflammation, insulin sensitivity and weight loss provided by GLP-1 RA providing greater fat loss without hyperglycemia. Additional data on noninvasive assessments of effectiveness to determine whether the drug should be continued to avoid liver biopsy, how long it should be continued, and the long-term sequelae of these agents are needed. Unlike treating other liver diseases like hepatitis C that only requires a defined course of treatment (8-12 weeks) with high cure rates (> 95%), MASH treatment may end up needing combinations of several drugs with different mechanisms [THR-β, incretins, and anti-fibrotics such as fibroblast growth factor 21 (FGF21) analogues] to reach comparable results. With our available data on incretin-based MASH treatment, it remains unclear if two are better than one.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

The graphical abstract was generated using Google Gemini. The author reviewed and finalized the content and took full responsibility for its accuracy and originality.

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Conflicts of interest

None.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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