Enhancing Treatment of Metabolic Dysfunction-Associated Steatohepatitis: Combination of GLP-1R Agonist with Others

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INTRODUCTION

Metabolic Associated Steatotic Liver Disease (MASLD) affects over one-quarter of people worldwide and is an increasingly important public-health problem. About 20–30% of those with MASLD progress to Metabolic Associated Steatohepatitis (MASH), a more severe condition marked by hepatic steatosis, inflammation, fibrosis, and hepatocyte ballooning [1]. MASH arises from complex, multi-factorial pathogenic processes—often described as “multiple hits”—that involve dysregulated lipid handling, immune activation, and insulin resistance. Recent drug development has targeted these diverse pathways, but therapeutic options remain limited. For example, the THR-β agonist MGL3196, the first approved agent, achieves histologic resolution in only about 30% of patients [2]. The GLP-1 receptor agonist semaglutide has also gained regulatory approval for MASH and represents the second US FDA–approved treatment in this indication [3]. Because MASH pathogenesis is multifaceted, combination regimens that address multiple mechanisms may improve efficacy, potency, and tolerability.

AIM

This study aims to explore the therapeutic potential of the GLP-1R agonist and the GLP-1/GIP/glucagon receptor triple agonist, in combination with THR-β agonist and FGF21 analog in HFD+CCl4-induced murine model of MASH. Whether multi-targeted therapy yields superior histologic and metabolic benefit in comparison with semaglutide mono therapy group.

METHODS

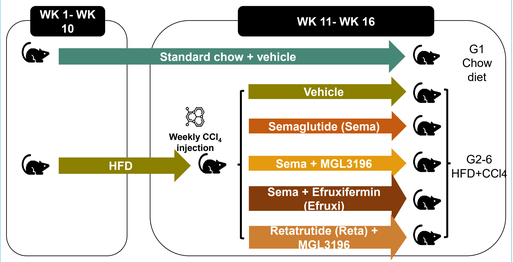

Figure 1. Generation of MASH Mouse Model and Treatments

C57BL/6J mice were fed a high-fat diet (HFD) for 10 weeks, with weekly intraperitoneal (i.p.) injections of CCl4 to induce MASH. Following this, semaglutide and various combination therapies were administered for 6 weeks.

RESULTS

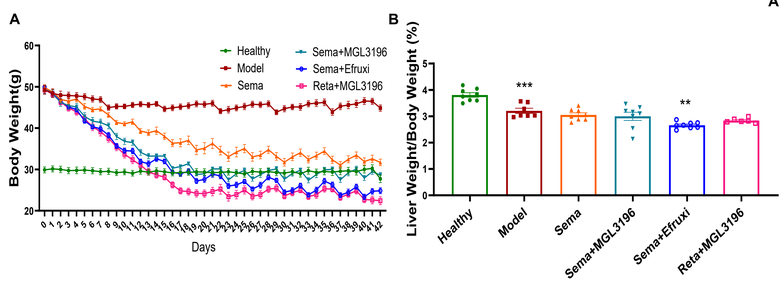

Figure 2. Semaglutide and Combination Therapies Reduces Body Weight

(A) Daily body weight record. (B) Liver weight to body weight ratio.

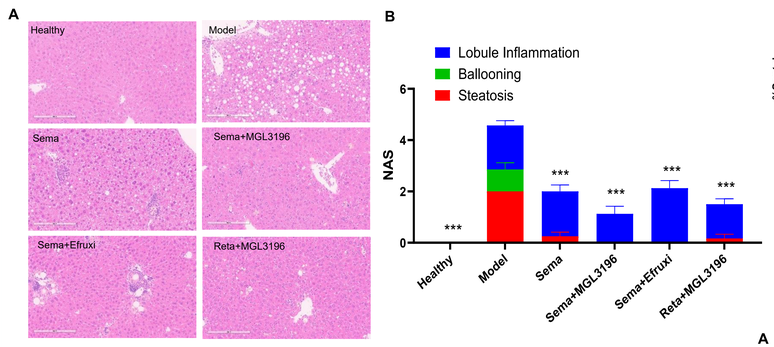

Figure 3. Semaglutide and Combination Therapies Alleviates NAFLD Progression

(A) Representative HE staining results. (B) NAS score including steatosis, ballooning and inflammation.

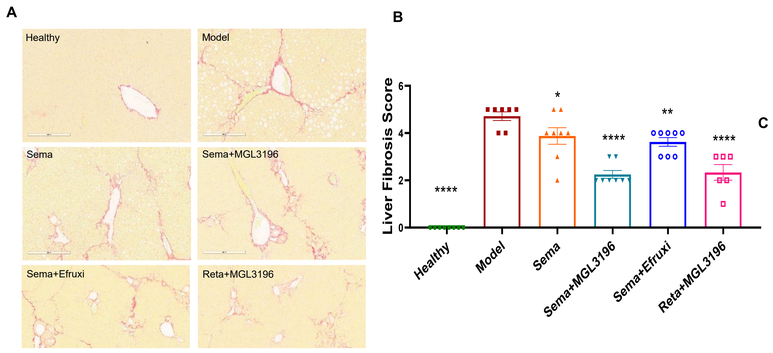

Figure 4. Semaglutide and Combination Therapies Alleviates Liver Fibrosis

(A) Representative Sirius Red staining results. (B) Liver fibrosis score.

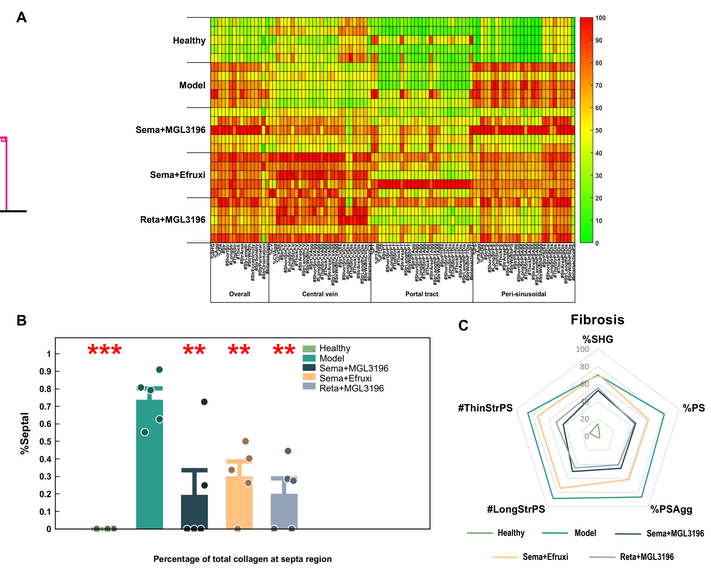

Figure 5. LiverIndex Analysis of Effects of Combination Therapies on MASH

(A) Heatmap showing fibrosis results in different liver sections. (B) Fibrosis Septa results showing bridging fibrosis. (C) Fibrosis radar map showing portal area fibrosis.

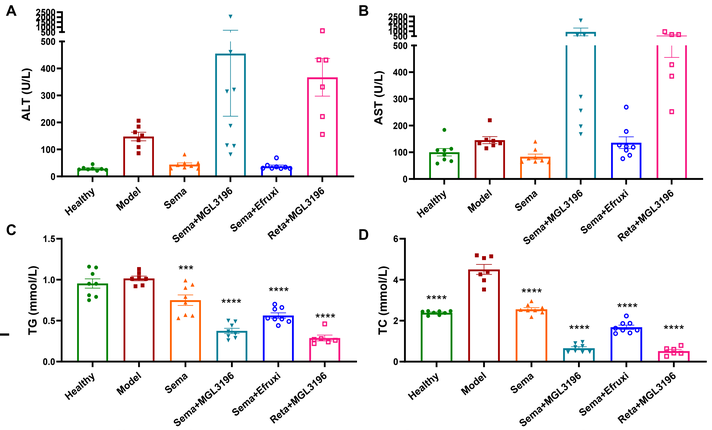

Figure 6. Effects of Combination Therapies on Serum Markers in MASH

Serum profiles showing (A) alanine aminotransferase (ALT), (B) aspartate aminotransferase (AST), (C) triglycerides (TG), and (D) total cholesterol (TC) levels following treatment.

CONCLUSIONS

1. All treatments were effective, with combination therapies producing larger effects. Sema+Efruxi and Reta+MGL3196 led to greater reductions in liver-to-body weight ratios, indicating improved metabolic status.
2. Every treatment significantly lowered NAS and fibrosis scores. The GLP-1R agonist + MGL3196 combinations achieved the largest gains, particularly reducing periportal fibrosis.
3. All interventions decreased hepatic and serum triglycerides and total cholesterol. Sema alone and Sema+Efruxi also improved liver enzymes and lipid metabolism, providing broader hepatic protection.
4. AST and ALT levels rose with combined GLP-1R agonist and MGL3196 treatment.
5. The results suggest that multiple combination therapies improve both metabolism features and liver pathology in MASH mouse model.

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