Differential anti-fibrotic effects of semaglutide and lanifibranor demonstrated by AI-digital pathology in the biopsy-confirmed GAN DIO-MASH mouse model with advanced fibrosis and HCC

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INTRODUCTION

Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH), increases the risk for the development of liver fibrosis which may progress to cirrhosis and hepatocellular carcinoma (HCC). Semaglutide (glucagon-like-receptor 1 agonist) and lanifibranor (pan-peroxisome proliferator-activated receptor agonist) are currently in late-stage clinical development for fibrosing MASH.

AIM

The present study aimed to evaluate the efficacy of semaglutide and lanifibranor monotherapy on disease progression in the GAN diet-induced obese (DIO) model with biopsy-confirmed advanced fibrosing MASH and HCC (GAN DIO-MASH-HCC), using both stain and stain-free artificial intelligence (AI)-digital pathology.

MATERIAL & METHODS

Paired-biopsy samples from the GAN DIO-MASH-HCC model (54 weeks of diet) treated for 14 weeks with either vehicle, 30 mg/kg lanifibranor or 30 nmol/kg semaglutide (N=15-17 animals/group) were included. Histopathological NAFLD Activity Score and Fibrosis Stage were first evaluated by Gubra Histopathological Objective Scoring Technique (GHOST) AI-deep learning-based image analysis on HE and PSR stained images. Next, more nuanced features of fibrosis and steatosis were also examined using stain-free images captured by Second-harmonic generation / two-photon excitation fluorescence (SHG/TPEF) microscopy (Genesis®200, HistoIndex Pte Ltd, Singapore) from formalin-fixed paraffin-embedded liver tissues, where AI-based algorithms recognized three zones, namely portal tract (PT), central vein (CV) and peri-sinusoidal (PS) for zonal analysis. Multiple parameters of steatosis and fibrosis, including their distribution, composition as well as co-localization changes, were quantified and compared among intervention groups.

RESULTS

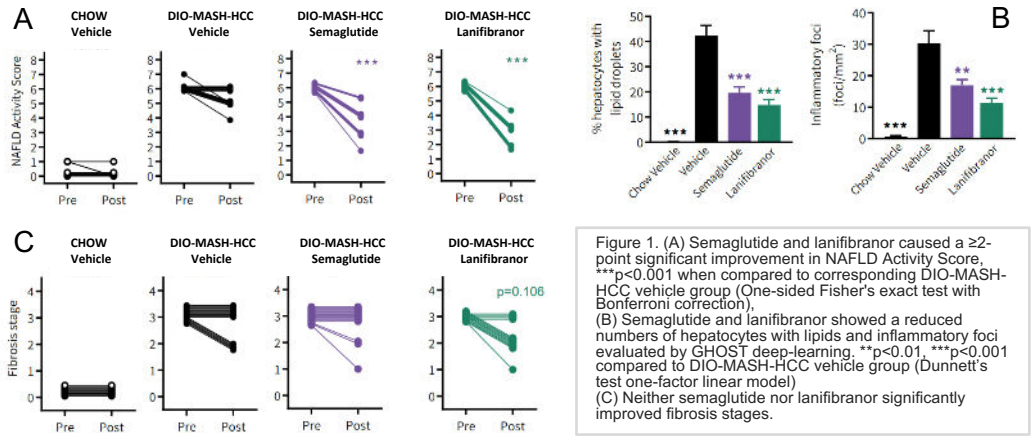

Figure 1. (A) Semaglutide and lanifibranor caused a ≥2-point significant improvement in NAFLD Activity Score, ***p<0.001 when compared to corresponding DIO-MASH-HCC vehicle group (One-sided Fisher's exact test with Bonferroni correction),
(B) Semaglutide and lanifibranor showed a reduced numbers of hepatocytes with lipids and inflammatory foci evaluated by GHOST deep-learning. **p<0.01, ***p<0.001 compared to DIO-MASH-HCC vehicle group (Dunnett's test one-factor linear model)
(C) Neither semaglutide nor lanifibranor significantly improved fibrosis stages.

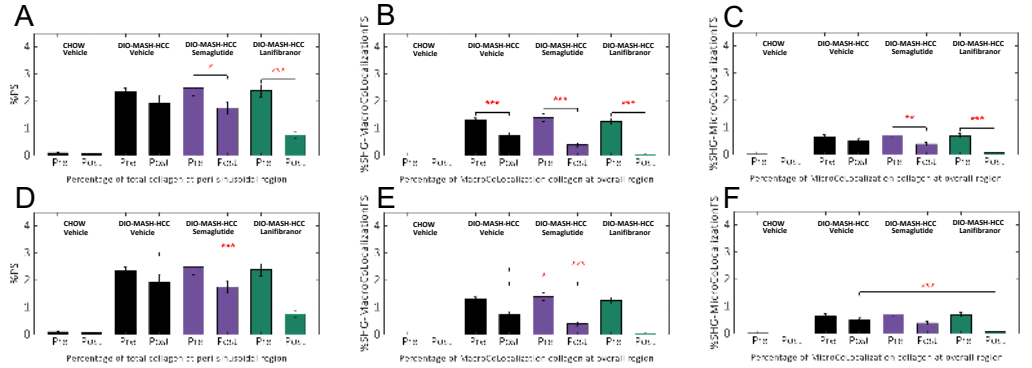

Figure 2. SHG/TPEF AI-based microscopy revealed that lanifibranor improved fibrosis in the PS zone and in the portion that is colocalized with both macro- and micro-steatosis, while semaglutide improved fibrosis more specifically in the area colocalized with macro-steatosis, which is one of the key features to characterize human NAFLD and is also the majority of steatosis found in this animal model. (A - C) Comparison of individual pre-pos (D-F) Comparison of DIO-MASH-HCC vehicle post-treatment post. (*p<0.05, **p<0.01, ***p<0.001. Two-tailed Student's t-test)

CONCLUSION

Our study demonstrated that stain-free AI digital pathology provides the sensitivity to detect differential fibrosis improvement in the GAN DIO-MASH-HCC mouse model treated with lanifibranor or semaglutide, which may have not been evident by fibrosis staging alone. Fibrosis zonal and co-localization analyses have the potential in providing insights into disease biology and drug mechanisms of action.

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DISCLOSURES

X.T, Q.Y and G.H are employees of HistoIndex or its subsidiary; D.A and A.A.B.A are employees of MSD; A.S, C.C and S.T are employees of Merck; M.H.N, S.E.P and M.F are employees of Gubra.

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