Characterization of disease progression and pharmacological intervention in the GAN diet-induced obese mouse model of NASH with advanced fibrosis and hepatocellular carcinoma

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Background & Aim

Pharmacological intervention targeting metabolic-associated NASH and hepatic fibrosis might also affect hepatocarcinoma (HCC). The GAN (Gubra-Amylin NASH) diet-induced obese (DIO) mouse model presents with key parameters of metabolic-associated NASH including moderate hepatic fibrosis. The present study aimed to characterize disease progression in the extended GAN DIO-NASH mouse model and evaluate treatment response for the late-stage clinical drug candidate elafibranor (PPAR-α/δ agonist).

Study outline

Histopathological NAFLD Activity Score and Fibrosis Stage

Histomorphometric steatosis, inflammation, fibrosis and tumor assessment

Hepatic transcriptomic profile for HCC

CONCLUSION

1. DIO-NASH mice demonstrated advanced NAFLD Activity Score (≥4) after ≥28 weeks on GAN diet.
2. DIO-NASH mice progressed to bridging fibrosis (stage F3) after ≥48 weeks on GAN diet.
3. DIO-NASH mice developed tumors including HCC after ≥58 weeks on GAN diet.
4. DIO-NASH mice demonstrated HCC-associated transcriptomic signature.
5. Elafibranor significantly improved NAFLD Activity Score and Fibrosis Stage in DIO-NASH-HCC mice.
6. Elafibranor reduced histological markers of steatosis, inflammation and fibrosis in DIO-NASH-HCC mice.
7. Elafibranor improved HCC-associated transcriptomic signatures in DIO-NASH-HCC mice.
8. The GAN DIO-NASH-HCC mouse model is suitable for profiling novel drug therapies for advanced fibrosis and HCC.