MET409, a potent, non-bile acid sustained FXR agonist, improves NAFLD Activity Score and exerts anti-fibrotic action in a diet-induced obese mouse model of biopsy-confirmed obese NASH with fibrosis

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INTRODUCTION AND AIM

The farnesoid X receptor (FXR) is a ligand activated transcription factor highly expressed in the liver and intestinal tract. Sustained FXR activation has shown efficacy in clinical trials for non-alcoholic steatohepatitis (NASH), notably in conjunction with anti-fibrotic action. The aim of this study was to explore the effect of MET409, a potent non-bile acid sustained FXR agonist, on metabolic, biochemical and histopathological endpoints in a diet-induced obese (DIO) mouse model of biopsy-confirmed NASH with fibrosis.

METHODS

Male C57BL6JRj mice were fed Gubra Amaryl NASH (GAN) diet high in fat, fructose and cholesterol for 15 weeks prior to liver pre-biopsy collection. Only animals with biopsy-confirmed steatosis (score ≥2) and fibrosis (stage ≥1) were included. Animals were stratified and randomized into treatment groups based on liver collagen 1α2 (% fractional area). DIO-NASH mice received vehicle (PO, QD), MET409 (3 mg/kg, PO, QD) and MET409 (10 mg/kg, PO, QD) for 8 weeks. Pre-post liver biopsy histopathology was performed for within-subject evaluation of changes in composite NAFLD Activity Score (NAS) and Fibrosis Stage. Also, terminal quantitative liver histology, blood and liver biochemistry was assessed.

STUDY DESIGN

Baseline characteristics in GAN DIO-NASH mice

MET409 treatment improves metabolic and biochemical parameters in GAN DIO-NASH mice

MET409 treatment improves NAFLD Activity Score in GAN DIO-NASH mice

CONCLUSION

- The GAN DIO-NASH mouse model exhibits metabolic disease and biopsy-confirmed hallmarks of NASH with fibrosis.
- Treatment with the non-bile acid sustained FXR agonist MET409 for 8 weeks:
  - Improved the metabolic and biochemical profile
  - Reversed steatohepatitis by histomorphometry
  - Improved composite NAFLD Activity Score (pre-to-post)
  - Improved Fibrosis Stage (pre-to-post)
  - Reduced fibrosis and hepatic stellate cell activation by histomorphometry
- FXR agonists, with similar profiles to MET409, are promising drug candidates for treatment of liver pathology by improving fibrosing NASH and preventing fibrogenesis.

*Balali et al., Gastroenterology 2019;156:1818. “Towards a standard diet induced and biopsy-confirmed mouse model of non-alcoholic steatohepatitis: impact of dietary fat source”. 