MGL-3196, a β-Selective Thyroid Hormone Receptor (THR) Agonist, Demonstrates Metabolic, Anti-inflammatory and Anti-fibrotic Benefits in a Long-term High Fat Diet (HFD) Mouse NASH Model

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INTRODUCTION

The hepatic THR-β receptor mediates the beneficial effects of thyroid hormone on LDL-cholesterol and triglycerides, fatty liver and insulin sensitivity. Studies show that hepatic hypothyroidism is present in human NASH. MGL-3196 is a liver-directed, oral, selective THR-β agonist in Phase 2 for treatment of NASH. MGL-3196 is highly protein bound (~98%) with high liver uptake and low extrahepatic permeability. In C57BL6 mice treated with 600 mg/kg HFD for 38 weeks, MGL-3196 reduced cholesterol and ALT without the adverse effects of T3, which showed THRA mediated bone loss in the 3 week treatment.

AIM

To demonstrate the liver-directed pharmacologic effects of MGL-3196 in a mouse NASH model.

MATERIALS & METHODS

Mice on a HFD for 17 or 36 weeks were treated by daily oral gavage for 24 or 24 days with 0.3 or 3 mg/kg/day of MGL-3196 (Figure 2, 7 panel RI). Mice on a HFD or normal chow (lean) or HFD plus oral admixture of 0.1, 0.3, 1.0 or 3 mg/kg day MGL-3196 or 3 mg/kg/day rosiglitazone were treated for 25 weeks (Table 1, Figures 3-6, 7 Panel L). Mice were sacrificed and liver samples were processed and total RNA was extracted. Gene array studies were conducted using Illumina chips. At sacrifice blood samples were collected for clinical chemistry and lipid levels.

RESULTS

MGL-3196 is specifically taken up into the liver by hepatic transporters (Figure 1). Metabolic effects of MGL-3196 treatment for 24 days (Figure 2; 7R) or 25 weeks (Table 1, Figures 3-7) included elimination of steatosis, normalization of liver size with no effect on overall body weight, improved insulin sensitivity, reduction in ALT (46%), free fatty acids (30%), and cholesterol (67%). Gene expression arrays confirmed regulation of known THR-β target genes such as Deiodase 1, malce enzyme and FGF-21 (Figures 3). Metabolic genes associated with lipotoxicity such as acetyl CoA-carboxylase (ACC1) and 11 β Hydroxysteroid Dehydrogenase (HSD) were also normalized. In 25 week studies (Fig. 7, panel L) inflammatory (chemokine ligand 2 (CCL2), other chemokines) and major fibrosis associated genes (tissue inhibitor metalloproteinase (TIMP1), smooth muscle actin (SMA), connective tissue growth factor (CTGF) and collagen genes), were significantly increased in HFD as compared with lean controls and were normalized to the level of the lean control mice by treatment with human-relevant doses (0.3-3 mg/kg) MGL-3196 but not rosiglitazone which had a modest effect (Figure 7). In 24 day treatment of HFD mice (Fig. 7, panel RI), a similar reduction of NASH inflammatory and fibrosis transcripts was observed.

CONCLUSIONS

• These results confirm that prolonged treatment of mice with MGL-3196 improved NASH profile consistent with activation of THR-β and fibrosis pathways.
• MGL-3196 potentially normalizes hepatic function in HFD animals, including restoration of normal metabolic homeostasis without impacting tissues outside the liver.
• At human equivalent exposures MGL-3196 appears to reverse and prevent progression of lipid, inflammatory and fibrotic markers of NASH.

REFERENCES

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DISCLOSURES

Rebecca Taub - Management Position: Madrigal Pharmaceuticals
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