Elafibranor and pioglitazone reduce NASH and fibrosis in a genetically-obese dietary induced NASH mouse model

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Introduction and Aim

Many animal models of non-alcoholic steatohepatitis (NASH) have been developed which mirror various aspects of the disease and choosing the most appropriate is a key question faced by the pharmaceutical industry. Dietary-deficient mouse models of NASH present limitations due to their associated weight loss resulting in an altered metabolic profile to man. To resolve this issue we have developed a genetically-obese dietary-induced mouse model (ob/ob H-FFC) of NASH and fibrosis which is more congruent with man. We have evaluated this paradigm with the clinically effective dual peroxisome proliferator activated receptor (PPAR)α/δ agonist elafibranor and the PPARγ agonist pioglitazone.

Methods

Male ob/ob mice were maintained on standard chow or a high-fat/fructose/cholesterol (H-FFC) diet for 12 weeks. Niche were randomised into treatment groups and received either vehicle (pe), pioglitazone (15 mg/kg po bid) or elafibranor (20 mg/kg po qd) from the first day of the diet induction. A blinded histopathological assessment of the individual and combined components of the NAFLD activity score (NAS; steatosis, hepatocellular ballooning and lobular inflammation) and fibrosis was performed. Additionally, plasma parameters and liver lipids and collagen were quantified.

Study Design

Figure 1

Baseline Dosing / Randomisation

Week 0

In vivo dose/phase

Histology/Analysis

Week 12 chow or H-FFC diet

Liver histology: NAS and fibrosis
Liver histology: Collagen, Cholesterol,
Liver histology: Glucose, Insulin,
Liver histology: Collagen and NAS

Results

Figure 2

Liver histology scoring and representative images ob/ob H-FFC mice.

Scoring of steatosis (NAS), hepatocellular ballooning (HIC), lobular inflammation (LIC) and fibrosis (F) was performed by Renasci. NAS activity score (NAS) is defined by combination of the steatosis, hepatocellular ballooning and lobular inflammation scores. Data are presented as means and S.E.M. Significant differences versus the chow group are denoted by *p<0.05, **p<0.01 and ***p<0.001 and versus the H-FFC vehicle group are denoted by †p<0.05, ††p<0.01 and †††p<0.001.

Figure 3

Liver histology scoring and representative images ob/ob H-FFC mice.

Representative images of NAS and LIC stained liver at 10× magnification are shown.

Conclusions

• Renasci's ob/ob H-FFC mouse exhibits NASH and fibrosis.
• The clinically effective agents pioglitazone and elafibranor reduce NASH and fibrosis in the ob/ob H-FFC mouse.
• Liver collagen and plasma ALT were significantly increased in the ob/ob H-FFC mouse and this increase was inhibited with treatment with either pioglitazone or elafibranor.
• A small reduction (-3 to -7%) in body weight is observed when ob/ob mice are maintained on the H-FFC diet. As reported in the clinic pioglitazone increased body weight and elafibranor decreases body weight.
• The ob/ob H-FFC mouse presents a useful tool for assessing potential new therapies for NASH and fibrosis which translates to efficacy in the clinic.