RDX023-2, a minimally systemic, non-bile acid FXR agonist, reduces steatosis, inflammation and fibrosis in three mouse models of NASH

Andrew J King, Jianhua Chao, Rakesh Jain, Lily Hu, Patricia Finn, Kenji Kozuka, Matthew Siegel, Ying He, Samantha Koo-McCoy, Qumber Jafri, David Rodriguez, Zhengfang Jiang, Limin He, Jeremy S Caldwell

Ardeleyx, Inc., Fremont, CA, USA

Background

The farnesoid X receptor (FXR) is a ligand-regulated transcription factor highly expressed in the liver and intestine that regulates bile acid, lipid and glucose homeostasis. FXR is activated by endogenous bile acids, but can also be modulated by synthetic ligands. Systemic FXR agonists have shown therapeutic promise in non-alcoholic steatohepatitis (NASH) but may have adverse effects. FXR agonists that target the key pharmacologically responsive tissues (intestine and liver) with minimal systemic exposure may have reduced side effects compared with systemic agonists. Here, we characterize RDX023-2, a potent, selective, non-bile acid, minimally systemic FXR agonist, and its effects in three mouse models of NASH.

Methods

Pharmacokinetic and pharmacodynamic studies were performed in male C57Bl/6 mice following a single oral dose of RDX023-2. FXR target gene expression was measured by quantitative polymerase chain reaction (qPCR) with a high dose of LJN452, a potent, systemic FXR agonist, as a positive control. β-actin was used as a reference gene. Administration of RDX023-2 in three mouse models of NASH

● Six-week-old male C57Bl/6 mice were acclimated on a Western diet (WD; TD 88137, Teklad) for 4 weeks (WD model).
● Six-week-old male ob/ob mice were acclimated on a NASH-promoting diet high in trans-fat, cholesterol and simple carbohydrates (D09100301, Research Diets) for 6 weeks (HFCD model).
● Six-week-old male ob/ob mice were acclimated on the NASH-promoting diet high in trans-fat, cholesterol and simple carbohydrates (D09100301, Research Diets) for 6 weeks (HFCD model).

Assessment of the effects of RDX023-2 administration

● Plasma and hepatic lipids, hepatocellular injury enzymes (ALT, aspartate transaminase (AST), β-hydroxybutyric acid (β-HBA), histone and fibrinogen content were measured.

Statistical significance was determined by analysis of variance (ANOVA).

Liver histology was performed by an external blinded pathologist.

RNA was extracted from liver samples for library preparation and RNA sequencing.

Results

Pharmacokinetics and pharmacodynamics

● Oral administration of RDX023-2 (3 mg/kg) resulted in a minimally systemic pharmacokinetic profile (maximum concentrations in plasma: 5 ng/ml, with maximum drug concentrations measured in the ileum (4470 ng/g) and liver (64 ng/g).

Administration of RDX023-2 resolved hepatic steatosis and hepatocellular injury in the HFCD model (Figure 3). Administration of RDX023-2 in an ob/ob mouse model of NASH

● Normalized liver triglycerides and liver and plasma cholesterol concentrations at a dose of 1 mg/kg.

Increased plasma concentrations of FGF19 and total cholesterol were measured in the ileum (4470 ng/g) and liver (64 ng/g).

Administration of RDX023-2 resolved liver triglycerides and plasma cholesterol concentrations at a dose of 1 mg/kg.

Increased plasma concentrations of FGF19 and total cholesterol were measured in the ileum (4470 ng/g) and liver (64 ng/g).

Liver inflammation, fibrosis and steatosis after administration of RDX023-2 in a HFCD mouse model of NASH

● Normalized liver AST and ALT concentrations and increased plasma concentrations of FGF15, leading to normalization of serum bile acid levels.

Administration of RDX023-2 decreased liver concentrations of pro-inflammatory cytokines and the fibrosis marker hydroxyproline, which were elevated in HFCD mice compared with non-treated controls (Figure 5).

Liver histology showed that RDX023-2 decreased both macrovesicular and microvesicular steatosis (Figure 5).

RNA sequencing analysis in ob/ob and HFCD mouse models of NASH

Both ob/ob and HFCD mice showed transcriptional dysregulation of lipid metabolism, pro-inflammatory and pro-fibrotic genes, which was alleviated by treatment with RDX023-2 (Figure 6).

Effects of RDX023-2 in an in vitro cellular model of human ileum

RDX023-2 showed similar potency in human and mouse transductions FGF secretion assays (Figure 7).

Conclusions

● RDX023-2 is an efficacious, minimally systemic, non-bile acid FXR agonist that effectively reduced hepatic steatosis in three mouse models of NASH.

● Effects on hepatocellular-related end points were comparable to those elicited by a potent, systemic FXR agonist.

● Administration of RDX023-2 was associated with reduced liver inflammation and fibrosis, and normalization of liver gene expression patterns.

● The effects of RDX023-2 on basal and stimulated FGF19 secretion in an in vitro model of the human ileum suggest translational potential.

These results suggest that a minimally systemic FXR agonist such as RDX023-2 could be useful for the treatment of patients with NASH, with the potential for fewer side effects than systemic FXR agonists.

References


Acknowledgments

Medical writing support was provided by Sarah Grotens, PhD, of PharmaGenesis Limited, London, UK and funded by Ardeleyx.

Disclosures

This study was funded by Ardeleyx. All authors are current or former employees of Ardeleyx.

Presented at Digestive Disease Week, June 2-5, 2018, Washington, DC, USA