FXR agonist Px-102 improves hepatic steatosis in NAFLD mouse models

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Abstract

FXR (NR1H4), a nuclear bile acid receptor, plays a major role in controlling hepatic lipid, cholesterol and carbohydrate metabolism (Ref 1,2). Currently FXR agonists are in advanced clinical studies as a novel pharmacotherapy for liver diseases such as NAFLD, NASH or Primary Biliary Cirrhosis (PBC). We have developed a novel synthetic FXR agonist, Px-102, which displays drug like pharmacokinetics in various animal models and humans. Px-102 is now entering Phase II clinical studies to determine whether this FXR agonist can reduce hepatic lipid accumulation in human NAFLD patients. Thus, we sought to analyze the impact of this drug in comparison to the other clinical stage FXR agonist 6-Ethyl CDCA (6-ECDCA or Obeticholic Acid) on liver lipid metabolism, hepatic steatosis and plasma clinical chemistry in mouse models of Metabolic Syndrome and NAFLD.

C57Bl/6J mice were prefed on a High Fat High Cholesterol diet (HFHCD) or on a High Fat High Cholesterol diet plus Fructose (HFHCD + Fructose) and then treated with Px-102 and 6-ECDCA for either 2 weeks or 4 months. Px-102 and, to a lesser extent, 6-ECDCA showed substantial plasma cholesterol and triglyceride lowering paralleled by a massive reduction of hepatic triglycerides and cholesterol. Px-102 reduced the expression of SREBP-1c and Malic Enzyme 1 both of which are involved in hepatic de novo lipogenesis, but at the same time increased expression of Fatty Acid Synthase (FAS) and genes involved in cholesterylcerogenesis. Thus, it is unlikely that FXR agonists reduce steatosis only by liver-centric reduction of lipogenesis pathways but potentially also by downregulating intestinal lipid uptake.

In summary, Px-102, a novel synthetic FXR agonist improves Metabolic Syndrome associated liver steatosis and hyperlipidosis indicating that this drug might be a good candidate to treat human NAFLD.

Materials & Methods:

Since we aim in developing an FXR agonist, Px-102 (old research code = Px20606) for the treatment of NAFLD and NASH, we investigated if Px-102 was able to reduce liver steatosis in mouse models of metabolic syndrome and fatty liver disease such as C57Bl/6J mice on various High Fat Diets or CETP/Kd mice on a Western diet. All these animal models present with a significant degree of liver steatosis and varying degrees of plasma hyperlipidemia and hypercholesterolemia.

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In summary, Px-102, a novel synthetic FXR agonist improves Metabolic Syndrome associated liver steatosis and hyperlipidosis indicating that this drug might be a good candidate to treat human NAFLD.

Results: