Aramchol™ Reduces Established Fibrosis in MCD Diet Animal Model

M. Varela-Rey\(^1\), D. Fernández-Ramos\(^1\), M. Irurzunaga-Lejarreta\(^1\), S. Van Liem\(^1\), L. Cruz-Villar\(^1\), S. López de Dávalillo\(^1\), L. Martín-Ruíz\(^1\), I. Aurekkoetxea\(^1\), X. Buque\(^1\), J. Lavín\(^1\), A. Aranaya\(^1\), L. Hayardeny\(^1\), C. Alonso\(^1\), J. Falcón\(^1\), P. Aspichueta\(^1\), J. Anguita\(^1\), J. Mata\(^1\)

\(^1\)CIC bioGUNE, CIBEREHD, GWL, CIC bioGUNE, Dermo, Spain; \(^2\)Facultad of Medicine and Nursing, University of the Basque Country (UPV/EHU), Leioa, Spain; \(^3\)Galmed Pharmaceuticals Ltd., Tel Aviv, Israel; \(^4\)CIC bioGUNE, CIBEREHD, Ikerbasque, \(^5\)CIC bioGUNE, Ikerbasque, Dermo, Spain.

INTRODUCTION
Nonalcoholic fatty liver disease (NAFLD) is the most common disease of the liver with a prevalence between 10-40% in Western countries. Its most severe form, Nonalcoholic steatohepatitis (NASH), defined by liver fat accumulation, inflammation and hepatocyte injury. NASH is a progressive disease that can eventually lead to further liver injury, advanced fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Aramchol™ (acarbil) amido chelanic acid) is a fatty acid-bile acid conjugate which has been shown to reduce liver fat content in patients with nonalcoholic fatty liver disease (NAFLD) and is presently in Phase 2b study (ARREST) for nonalcoholic steatohepatitis (NASH). Here we used a modification of the canonical MCD diet model by adding 0.1% methionine to the diet. This choline deficient diet containing 0.1% methionine (0.1MCD) diet) induces steatohepatitis, inflammation and fibrosis. Aramchol™ down regulates steatohepatitis, inflammation and fibrosis via down regulation of SCD1 and up regulation of Glutathione production and elevation of renal homoeostasis.

AIM
The aim of this work was to investigate the mechanism of action of Aramchol™ and its potential effect on steatohepatitis and fibrosis using the 0.1% methionine- and choline-deficient (0.1MCD) diet mouse model of NASH.

METHOD
Mice were fed the Methionine and Choline Deficient (MCD) and control diet and were sacrificed after 4 weeks. The MCD diet induces aminotransferase elevation and changes in hepatic histological features, characterized by steatosis, local inflammation, hepatocyte necrosis and fibrosis. These changes occur rapidly and are morphologically close to those observed in human NASH. In this study the MCD diet contained 0.1% methionine to minimize and stabilize weight loss. At the end of the second week, after verification of established NASH, 0.1MCD-fed mice were treated orally by gavage with Aramchol™ (5 mg/kg/day) or vehic (n=10, each condition). Control diet-fed mice were also treated with vehicle for same duration (n=10). At the end of the experiment, blood and liver samples were obtained.

RESULTS

**Effect of ARAMCHOL™ on Liver Steatosis in 0.1MCD Diet (histology - sudan III)**

- Normal Diet
- 0.1 MCD Diet
- 0.1 MCD Diet w/m Aramchol™

**Effect of ARAMCHOL™ on Collagen Production Liver Extract from 0.1MCD Mice**

- Treatment with ARAMCHOL™ significantly down regulates steatosis in the liver

**Effect of ARAMCHOL™ on Macrophages Activation and Infiltration in 0.1MCD Diet (F4/80 and CD64)**

- Normal Diet
- 0.1 MCD Diet
- 0.1 MCD Diet w/m Aramchol™

**Effect of ARAMCHOL™ on Collagen Production from LX-2 Human Hepatic Stellate Cells**

- Treatment with ARAMCHOL™ significantly down regulates/normalizes infiltration and activation status of macrophages in the liver

**Effect of ARAMCHOL™ on Fibrosis in 0.1MCD Diet (histology – sirius red)**

- Normal Diet
- 0.1 MCD Diet
- 0.1 MCD Diet w/m Aramchol™

**Effects of ARAMCHOL™ on Liver Biochemistry in 0.1MCD Mice**

- Treatment with ARAMCHOL™ significantly down regulates fibrosis in the liver

**ARAMCHOL™ significantly up regulates Glutathione and elevates GSH/GSSG ratio in 0.1 % MCD mice**

CONCLUSIONS
- Aramchol™ has an effect on the three main pathologies of NASH, steatosis, inflammation and fibrosis.
- Aramchol™ down regulates collagen production from human stellate cells.
- Aramchol™ effects are mediated through down regulation of SCD1 and up regulation of Glutathione production.
- The data suggest that the effect of Aramchol™ on fibrosis is mediated via down regulation of steatosis and inflammation and also direct via down regulation of collagen production from stellate cells.
- These results suggest potential effects of Aramchol™ on fibrosis in NASH patients.

CONTACT INFORMATION
Prof. Jose M. Mato, General Director of CIC bioGUNE and CIC biomaGUNE in the Basque Country: director@cibicigune.es

REFERENCES

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