A novel small molecule modulating the mitochondrial NEET proteins improves inflammation and fibrosis in liver and kidneys of NASH mice

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INTRODUCTION

Non-alcoholic steatohepatitis (NASH) is a disease characterized by excessive fat accumulation, inflammation, and ballooning degeneration of hepatocytes, with or without fibrosis in the liver. It is now reported that NASH not only affects the liver but is also associated with chronic kidney disease (CKD). However, the morphological appearance of NASH kidneys has been poorly characterized. These observations highlight the need for a treatment that targets both conditions. Here, we assessed the effect of a novel chemistry that regulates the function of 3 mitochondrial proteins called the NEET proteins, previously reported to be important in metabolic diseases, on a diet-induced NASH model in mice.

OBJECTIVES

Characterize dEF3122, a novel small molecule modulating the mitochondrial NEET proteins, in a mouse model of NASH in comparison to Obeticholic acid (OCA). Liver and kidney histological features improvements will be described.

METHODS

Five-week-old male C57BL/6JRj mice were fed either chow diet or AMLN diet (40% total fat kcal of which 18.5% were trans-fat kcal, 20% fructose, 2% cholesterol). This diet was maintained for 29 weeks prior to study initiation. Three weeks prior to study initiation, liver biopsies were taken and animals with steatosis grade <2 and fibrosis stage <1 were deselected from the study. Prior to first administration of test article, stratified randomization of mice into treatment groups was performed according to collagen 1a1 (IHC) morphometry from the week -3 biopsies. Each treatment group consistent of 12 mice. For a total of 8 weeks, compound dEF3122 was administered orally, twice daily at a concentration of 7mg/kg or 20mg/kg, and OCA was administered orally, once daily at a concentration of 30mg/kg. At the end of the treatment animals were sacrificed, livers and kidneys were collected, and sections were stained with H&E, PAS and picrosirius red (PSR) to analyze their morphology. Histopathological analysis was performed by a pathologist blinded to the study. Fibrosis has been evaluated by quantification of the PSR positive areas. Inflammation has been graded by counting the H&E positive inflammatory foci per field.

RESULTS

NEET Modulator Improves Liver Histology in Periportal Region

Figure 1: Liver Portal Inflammation

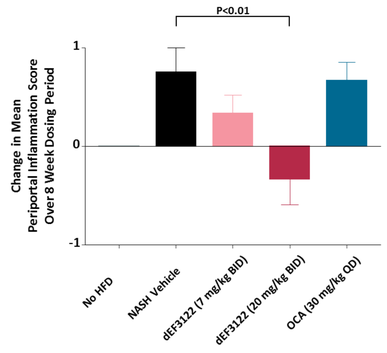


Figure 2: Liver Periportal Fibrosis

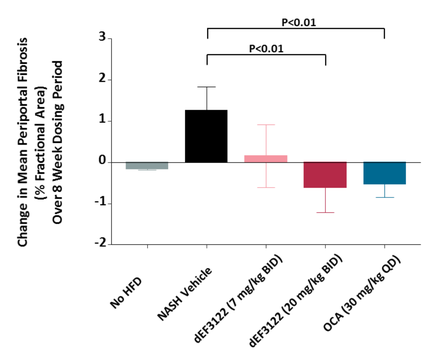
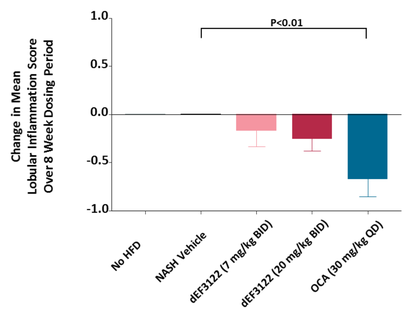


Figure 3: Liver Lobular Inflammation



NASH mice presented severe liver lesions such as steatosis, inflammation, and fibrosis. Therapeutic administration of dEF3122 was shown to resolve both inflammation and fibrosis in a dose-dependent manner, specifically in the periportal region (Figures 1 and 2) that has been identified as a marker of disease severity. On the opposite, OCA treatment results in a significant anti-inflammatory effect in the lobular region (Figure 3) but not in the portal/periportal region (Figure 1). NASH mice displayed also severe renal lesions such as tubular lipid accumulation, inflammation and interstitial fibrosis. dEF3122 was also able to completely resolve fibrosis and attenuate inflammation (50% decrease) in the kidneys (Figures 4 and 5), OCA displaying no effects on renal fibrosis (Figure 4).

NEET Modulator Improves Renal Histology

Figure 4: Renal Fibrosis

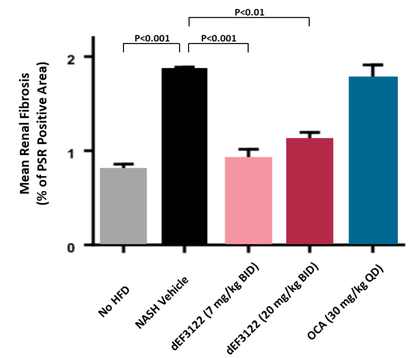
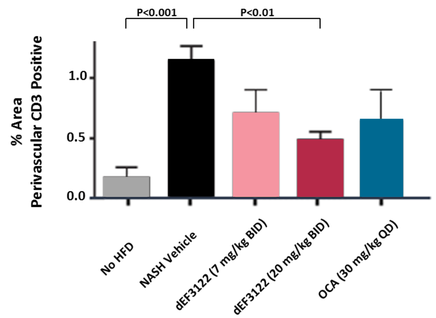


Figure 5: Renal Inflammation



No HFD | NASH Vehicle | dEF3122 (7 mg/kg BID) | dEF3122 (20 mg/kg BID) | OCA (30 mg/kg QD)

CONCLUSIONS

We have identified a new treatment that protects NASH mice from the development of both liver and renal lesions. Our molecule offers a novel approach for regulating the activity of a family of proteins of critical importance in mitochondrial biology (NEET proteins) and could offer new perspectives in the treatment of NASH and other diseases with an important inflammatory component.

DISCLOSURES

JV : Stock Shareholder at Obseva SA and Hoffman La Roche AG, Board member at Obseva SA, Inatherys SAS and Step Pharma SAS.

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