COMBINATION DRUG THERAPY ALLOWS SYNERGISTIC THERAPEUTIC DOSE REDUCTION IN NASH: A CASE STUDY OF ELAFIBRANOR (GFT505) AND AN FXR AGONIST COMBINATION IN A MODEL OF SEVERE NASH

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INTRODUCTION

Western lifestyle is invariably linked with high incidence rates of non-alcoholic steatohepatitis (NASH), a multifactorial, chronic liver disease that often progresses to liver fibrosis and cirrhosis and may ultimately lead to hepatocellular carcinoma [1, 2]. NASH has also been associated with increased occurrence of cardiovascular disease and other hepato-epithelial diseases [3].

Currently, there is no approved therapy for NASH. The treatment paradigm of drug combination has therefore emerged to provide the best possible therapy for the targeted NASH population. Similar approaches were previously tested in other multifactorial systemic diseases, such as hypertension, dyslipidemia or type 2 diabetes, where drug combinations showed a better control of the underlying disease and better long term patient adherence to the treatment.

In recent phase 2a studies, both elafibranor (ELA) and fibrate agents (metformin and bezafibrate) have shown efficacy on NASH and fibrosis [4, 5]. Since these drugs have complementary mechanisms of action, we compared their effects on pathological features of NASH and liver fibrosis in a model of severe disease [6] to assess potential therapeutic benefits of such combination therapy.

AIMS

To test the hypothesis that elafibranor and FXR agonist combination has synergistic effects on NASH development and to assess potential therapeutic benefits of such a combination therapy.

STUDY DESIGN

Male Wistar rats were randomly divided into 11 groups. (See Table 1 for groups composition).

Starting on day 0 and up to the end of the study, at the end of week 12, treated rats were fed a CDAA/c diet supplemented with the active substances: 

- elafibranor (ELA): 1mg/kg/day, 3mg/kg/day or 10mg/kg/day 
- OCA: 3mg/kg/day, 10mg/kg/day or 25mg/kg/day
- CSAA: 0.5, 1, 2, or 4mg/kg/day
- ELA+OCA: combination (3:1, 1:3 or 1:1)

Ratios treated with ELA+OCA were combinations of both control groups that received a CDAA/c diet and developed NASH pathology. NASH pathology and fibrosis development were scored by histology as described by Kleiner [8]. Additional biochemical and gene expression studies were also run to corroborate the histological outcomes.

Hepatic gene expression was studied by Affymetrix microarrays.

SYNERGY OF ELA AND OCA ON FIBROSIS DEVELOPMENT

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CONCLUSION

Wistar rats fed a CDAA/c diet developed severe NASH-related histology (advanced steatosis, lobular inflammation and ballooning) and fibrosis with high penetration rate.

Fibrosis development was significantly attenuated in animals that were administered with a high dose of Elafibranor (ELA) or Ocaftor (OCA) as single agent.

A synergistic effect on fibrosis attenuation was observed in animals that received ELA+OCA combination treatment as compared to single agents.

In contrast to fibrosis, there was no synergistic effect of ELA/OCA combination therapy on either ballooning or lobular inflammation and the effect of elafibranor was predominant on NASH histology.

ELA revealed a predominant effect on transcriptomic NASH signature as compared to OCA, although there was a significant overlap in the hepatic transcripts that were modulated by each agent.

IPA analysis showed that pathways related to liver metastasis, damage and regeneration responded better to ELA/OCA combination in this study.

Our findings suggest that ELA+FXR agonist combination treatment would benefit a wider patient population and possibly at lower therapeutic doses.

Plasma LBP

Oxidative stress markers

-Only genes with F2 and a values >1 were considered in this analysis. Analysis of hepatic PMAA and FXR target gene expression indicates that both molecular target classes (PMAA and FXR) were engaged. Within the goal of this work, the modulation of ELA and OCA combination is exemplified by liver LBP gene as compared to OCA (90% decrease) and by some genes modulated by both drugs. All genes were modulated exclusively by ELA/OCA administration.

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