varices requiring VH prophylaxis. (ClinicalTrials.gov number, NCT02649335.)

LBP-541

Hepatic fibrosis is associated with histological activity in nonalcoholic steatohepatitis: an analysis from a large database of screening biopsies in the CENTAUR trial

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Background and Aims: In nonalcoholic steatohepatitis (NASH), the main factor associated with hepatic outcomes is fibrosis progression. NASH is defined by liver cell injury (hepatocyte ballooning [BAL]), lobular inflammation (LI) and steatosis. Development of anti-inflammatory, antifibrotic or mixed agents for the treatment of NASH requires better understanding of the relationship between disease activity and fibrosis.
Methods: Screening liver biopsies from CENTAUR (NCT02217475; phase 2 trial of cenicriviroc versus placebo in subjects with NASH and fibrosis), were evaluated by a central pathologist. Those deemed adequate for pathological interpretation were included in this analysis (N = 557) regardless of study eligibility. Nonalcoholic fatty liver disease (NAFLD) activity score (NAS) and fibrosis stage were evaluated using NASH Clinical Research Network (CRN) classification. Portal inflammation (PI), LI and steatosis were each graded 0–3. Associations between histologic features were quantified by Spearman rank correlation and tested by the Fisher exact test.
Results: Rates of fibrosis stages 0,1,2,3, and 4 were 22%, 27%, 21%, 24% and 6%, respectively. For NAS, 28% of subjects had NAS ≤3, 23% had NAS = 4, 21% had NAS = 5, and 28% had NAS ≥6. Subjects with no cirrhosis showed an association between fibrosis stages and LI ($r = 0.41$), BAL ($r = 0.60$), and PI ($r = 0.55$). Subjects with moderate (Grade 2) or severe (Grade 3) LI had a prevalence of significant (stage ≥2) fibrosis of 57% versus 22% in those with no (Grade 0) or mild (Grade 1) LI ($p < 0.001$). Subjects with severe (Grade 2) BAL had a prevalence of 82% significant fibrosis versus 35% in those without BAL ($p < 0.001$). Subjects with moderate/severe PI had a prevalence of 78% significant fibrosis versus 23% in those with no/mild PI ($p < 0.001$). No strong association was found between fibrosis stage and steatosis grade. Alanine aminotransferase levels were higher with increasing grades of LI and BAL. Observed rates of moderate/severe LI and BAL were lower in subjects with cirrhosis compared to those with stage 3 fibrosis; moderate/severe PI progressively increased in all stages.
Conclusions: Histological features of hepatocellular injury and inflammation (but not steatosis) correlated with increasing fibrosis stages in NAFLD. If a new grading system is developed to replace NAS, a score with a wider range for BAL, LI, and PI, and de-emphasis of steatosis might be a better predictor of fibrosis progression and criterion of histologic response in clinical trials.

LBP-542

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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Background and Aims: Western lifestyle is invariably linked with high incidence rate 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. Currently, there is no approved therapy for NASH. In recent phase 2B studies, both elafibranor (ELA, PPARα/δ agonist) and obeticholic acid (OCA; FXR agonist) have shown efficacy on NASH and fibrosis. Since these drugs have complementary action mechanisms, we compared their action on pathological features of NASH to assess potential therapeutic benefits of combination therapy.
Methods: NASH histology and fibrosis were induced by feeding Wistar rats for 12 weeks with a choline-deficient L-amino-acid-defined-diet supplemented with cholesterol. Animals in the intervention groups, received either elafibranor (1, 3, or 10 mg/kg/day) or OCA (10, or 30 mg/kg/day) or combinations for the entire study period. NASH and fibrosis development were evaluated by histology. Additional biochemical and molecular analyses were also performed on different relevant biomarkers.
Results: Wistar rats fed the CDAA/chol diet developed histological features of NASH and fibrosis with high penetration of severe disease. ELA and OCA treatment alone dose-dependently attenuated fibrosis development (reduction of fibrosis area at the maximal tested dose was 77% and 53%, respectively). Combination treatment at submaximal doses (ELA 1 mg/kg/day + OCA 10 mg/kg/day) demonstrated a synergistic effect on fibrosis (fibrosis area diminished by 71%). Hepatocyte damage, i.e. ballooning, was prevented or attenuated by ELA in a dose-dependent manner. Instead, OCA only partially attenuated ballooning at the doses tested in this study. ELA, and to a lesser extent OCA attenuated lobular inflammation in a dose-dependent manner. In contrast to fibrosis there was no significant synergistic effect of combination therapy on either ballooning or lobular inflammation. Finally, the combination treatment of ELA with OCA revealed beneficial effects on different markers of tissue remodeling, inflammation, and oxidative stress.
Conclusions: The combination of ELA and OCA had synergistic anti-fibrotic effects in the CDAA/chol diet-induced NASH model. The therapeutic benefit was achieved at lower doses with the combination than with monotherapies. Our findings suggest that elafibranor/OCA combination treatment would benefit a wider patient population and at lower therapeutic doses.

LBP-543

iPLA2beta protects aged male mice from liver fibrosis and intestinal atrophy by modulating phospholipid and enterohepatic bile acid metabolism

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