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

V. Ratziu1, V.W.-S. Wong2, N. Lanthier3, J. Bourrier4, W. Alazawi5, J. Kluewe5, J. Genesca5, P. Andreone5, L. Serfaty6, R. Skoien6, B.L. Wiens7, P. Vig8, E. Lefebvre9, S. Seyedkazemi9, Z. Kayali2, F. Poordad10, A. Sanyal10, F. Tacke12, Z. Goodman10, Hôpital Pitié Salpêtrière and Université Pierre et Marie Curie, Paris, France;

Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong, Hong Kong, China;

Service d’Hépato-Gastroentérologie, Cliniques Universitaires Saint-Luc, Brussels, Belgium;

Hepato-Gastroenterology Department, University Hospital, Angers, France;

The Blizard Institute, Queen Mary, University of London, London, United Kingdom;

Department of Gastroenterology, Hamborg University Medical Center, Hamburg, Germany;

Hospital Universitari Vall d’Hebron, Barcelona, Spain;

Department of Medical and Surgical Science, University of Bologna, Bologna, Italy;

Department of Hepatology, Saint-Antoine Hospital, Paris, France;

Department of Gastroenterology and Hepatology, Royal Brisbane and Women’s Hospital, Brisbane, Australia;

ALLERGAN PLC, South San Francisco;

Inland Empire Liver Foundation, University of California Riverside, Rialto, California;

Department of Hepatology, Texas Liver Institute/University of Texas Health, San Antonio;

Department of Gastroenterology, Virginia Commonwealth University, Richmond, VA, United States;

Department of Medicine III, University Hospital Aachen, Aachen, Germany;

Center for Liver Diseases, Inova Fairfax Medical Campus, Fall Church, VA, United States

E-mail: Brian.Wiens@allergan.com

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 NAS 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, and 3 were 22%, 27%, 21%, 24% and 6%, respectively. For NAS, 28% of subjects had NAS ≥3, 23% had NAS ≤2, 21% had NAS = 3, and 28% had NAS ≥4. 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.