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A SPECIAL MEETING REVIEW EDITION

Highlights in Nonalcoholic Steatohepatitis (NASH) From Digestive Disease Week 2020

A Review of Selected Presentations From DDW 2020

Special Reporting on:

- Obeticholic Acid Improves Experimental Non-Invasive Markers of Non-Alcoholic Steatohepatitis and Advanced Fibrosis: Results of a Secondary Analysis From the Month-18 Interim Analysis of the REGENERATE Study
- Patients With Nonalcoholic Steatohepatitis (NASH) Have a Higher Prevalence of Myocardial Infarction
- Obesity-Specific Health-Related Quality of Life in Patients With Non-Alcoholic Steatohepatitis: Results From the REGENERATE Study
- Deleterious Impact of Advanced Nonalcoholic Steatohepatitis on Multiple Patient-Relevant Outcomes: An International, Cross-Sectional, Real-World Study
- Obeticholic Acid Improves Transaminases in Patients With Nonalcoholic Steatohepatitis: Results From the 18-Month Interim Analysis of the REGENERATE Study
- Identification of Significant Fibrosis in Patients With Nonalcoholic Steatohepatitis Using Noninvasive Tests: Determination of Optimal Thresholds Based on Cross-Sectional Analyses of Patients Screened for a Phase 3 Randomized Controlled Trial
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- Long-Term Safety Profile of Cenicriviroc in Adults With Nonalcoholic Steatohepatitis: Rollover Study

PLUS Meeting Abstract Summaries

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Obeticholic Acid Improves Experimental Non-Invasive Markers of Non-Alcoholic Steatohepatitis and Advanced Fibrosis: Results of a Secondary Analysis From the Month-18 Interim Analysis of the REGENERATE Study

Obeticholic acid is a potent, selective agonist of the farnesoid X receptor. In the ongoing phase 3 REGENERATE study (Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment), obeticholic acid improved liver fibrosis in patients with nonalcoholic steatohepatitis (NASH).[1] REGENERATE enrolled 2480 patients with biopsy-confirmed NASH, a nonalcoholic fatty liver disease (NAFLD) activity score (NAS) of at least 4, and stage 2 or 3 fibrosis. (Patients with stage 1 fibrosis were enrolled if they also had a comorbidity.) Patients were randomly assigned to receive obeticholic acid at 25 mg, obeticholic acid at 10 mg, or placebo. The 2 primary endpoints were fibrosis improvement by at least 1 stage with no worsening of NASH and resolution of NASH with no worsening of fibrosis. Study success was defined as the achievement of at least 1 of the primary endpoints.

Results from the prespecified 18-month interim analysis of the REGENERATE study were previously published.[1] This analysis provided data for the intention-to-treat population, which consisted of 931 patients with stage 2 or 3 fibrosis who received at least 1 dose of study treatment. The biopsy-based fibrosis improvement endpoint was achieved by 12% of patients in the placebo group, 18% of those in the 10-mg obeticholic acid group (*P*=.045), and 23% of those in the 25-mg obeticholic acid group (*P*=.0002).

Patients treated with obeticholic acid also showed improvements in results of established noninvasive tests of fibrosis, such as the aspartate aminotransferase/platelet ratio index (APRI), the fibrosis 4 (FIB-4) index, FibroSure, and FibroScan vibration-controlled transient elastography (VCTE).[2] A secondary analysis by Boursier and colleagues evaluated changes in 3 other noninvasive tests—FibroMeter, FibroMeter VCTE, and FibroScan-AST (FAST)—from baseline to month 18 among patients in the intention-to-treat population. At baseline, 419 patients were assessed by FibroMeter, 415 by FibroMeter VCTE, and 310 by FAST. The patients' characteristics were well balanced across the 3 arms. In the FibroMeter subset, the patients' median age ranged from 54.0 years to 55.8 years. The mean body mass index (BMI) was 5.6 kg/m^2 to 6.6 kg/m^2. Stage 3 fibrosis was reported in 52% to 60% of patients, and a NAS of grade 6 or higher was noted in 68% to 71% of patients. The mean alanine transferase (ALT) ranged from 51.4 U/L to 59.5 U/L, the mean aspartate transferase (AST) ranged from 33.0 U/L to 42.3 U/L, and the total bilirubin ranged from 0.63 mg/dL to 0.70 mg/dL. Across the 3 arms in the FAST subset, the patients' median age ranged

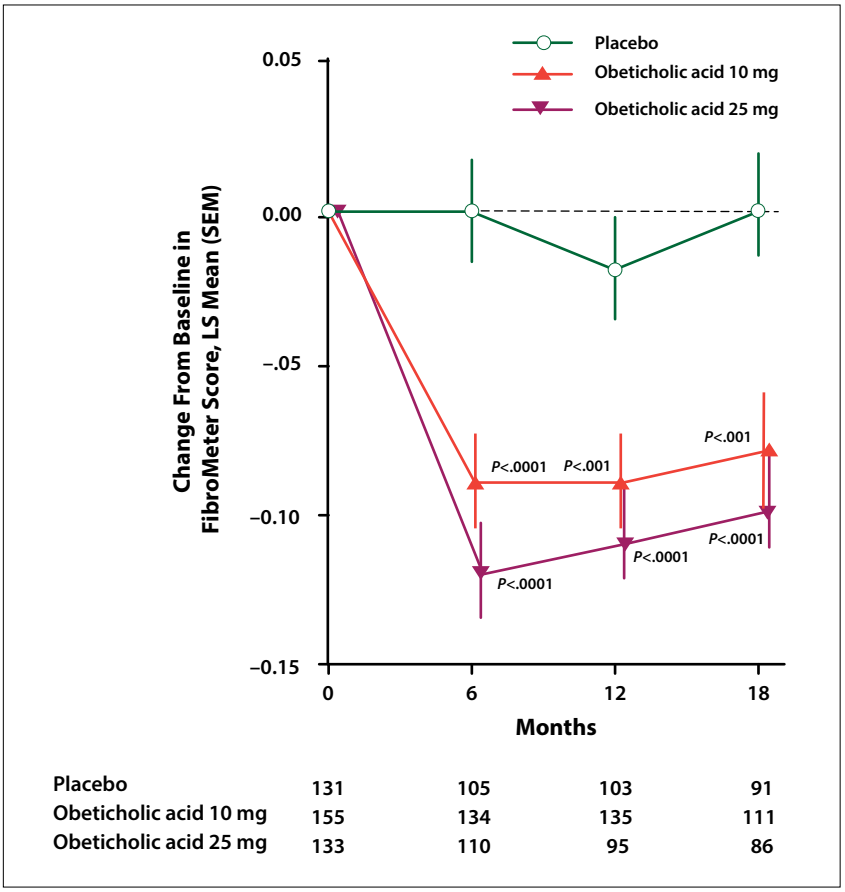

Figure 1. FibroMeter scores over time among patients in the intention-to-treat population of the REGENERATE trial. Results are shown for patients with FibroMeter scores at baseline. LS, least square; SEM, standard error of mean. Adapted from Boursier J et al. DDW abstract 334. *Gastroenterology.* 2020;158(6 suppl 1).[3]

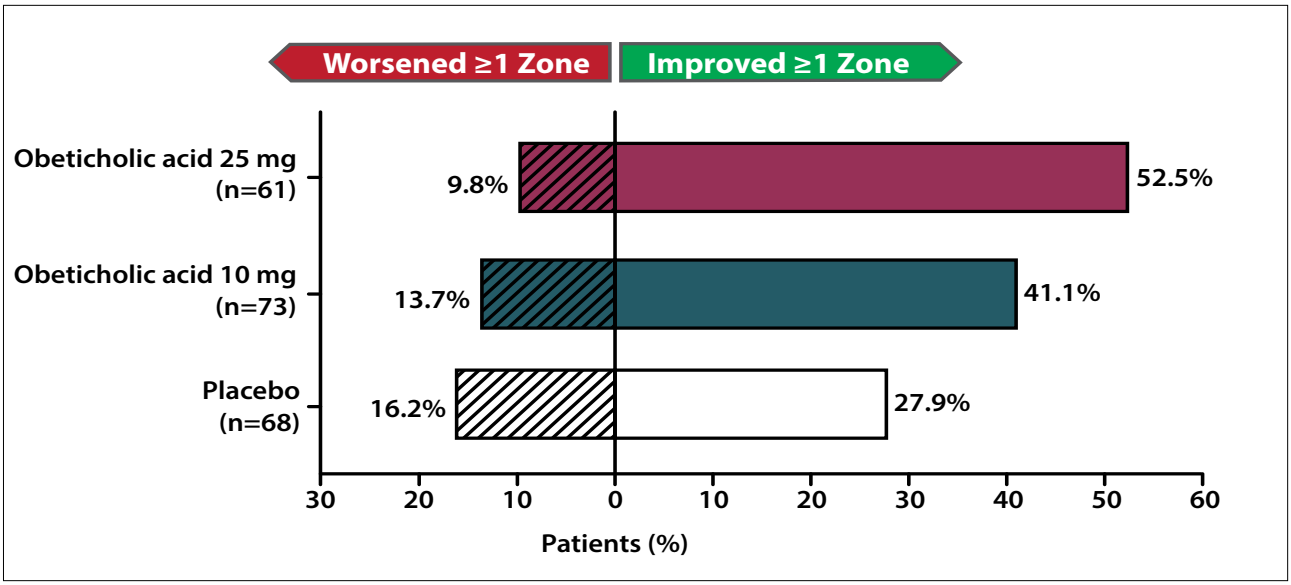

Figure 2. Changes in the FAST score from baseline to month 18 among the intention-to-treat population of the REGENERATE trial. Data are shown for patients with a FAST score at baseline and month 18. FAST, FibroScan-AST. Adapted from Boursier J et al. DDW abstract 334. *Gastroenterology.* 2020;158(6 suppl 1).[3]

from 54.8 years to 56.1 years. Stage 3 fibrosis was reported in 57% to 61% of patients, and a NAS of grade 6 or higher was observed in 64% to 73% of patients. The mean ALT was 49.0 U/L to 60.1 U/L, the mean AST was 32.4 U/L to 47.4 U/L, and the total bilirubin was 0.28 mg/dL to 0.34 mg/dL. At baseline, the mean and median noninvasive test scores were higher in patients with stage 3 fibrosis vs stage 2 fibrosis. There were no significant differences in the FibroMeter, FibroMeter VCTE, or FAST scores across treatment arms at baseline.

Improvement in the noninvasive test scores was superior with obeticholic acid compared with placebo after 6 months of treatment, with sustained reductions through 18 months of treatment (Figure 1). Both dose levels of obeticholic acid showed similar improvements in FibroMeter and FibroMeter VCTE scores. In contrast, with the FAST score, the higher dose of obeticholic acid yielded a greater improvement compared with the lower dose (Figure 2). In patients with stage 2 fibrosis at baseline, the FibroMeter score was reduced by a similar amount with both dose levels of obeticholic acid at 6 months through 18 months. However, among patients with stage 3 fibrosis, the higher dose of obeticholic acid showed a superior reduction compared with the lower dose at 6, 12, and 18 months. Both dose levels were superior to placebo. The FibroMeter VCTE score followed a similar pattern, with both dose levels of obeticholic acid yielding superior improvements vs placebo at 6, 12, and 18 months.

A study by Newsome and colleagues calculated the FAST score cutoff values that identify patients with fibrosis of stage 2 or higher and a high disease burden, defined as a NAS of 4 or higher.[4] The study found that a score of 0.67 or higher identified those patients with stage 2 or higher fibrosis and a NAS of 4 or higher. A score of 0.35 or lower excluded those patients. A FAST score between 0.35 and 0.67 was considered indeterminate. When these cutoff values were applied to patients in the REGENERATE study at 18 months, 52.5% of patients in the 25-mg obeticholic acid arm shifted by 1 zone of improvement, while 9.8% shifted by 1 zone of worsening. In the 10-mg obeticholic acid arm, 41.1% of patients improved by 1 zone, and 13.7% of patients worsened by 1 zone. In the placebo arm, 27.9% of patients improved by 1 zone, and 16.2% of patients worsened by 1 zone.

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Patients With Nonalcoholic Steatohepatitis (NASH) Have a Higher Prevalence of Myocardial Infarction

Both NAFLD and NASH are associated with metabolic syndrome and other risk factors for acute myocardial infarction. There are several potential pathophysiologic mechanisms of cardiovascular disease in NAFLD, such as systemic endothelial dysfunction, proatherogenic lipid profiles, and increased activation of hepatic and systemic inflammatory cascades. In a 2016 meta-analysis of approximately 34,000 patients with NAFLD, those with more severe disease had an odds ratio (OR) of 1.64 (95% CI, 1.26-2.13) for combined fatal and nonfatal acute myocardial infarction or stroke events.[1] In a prospective observational study of 898 consecutive patients, NAFLD increased the risk of cardiovascular events (hazard ratio, 2.41; 95% CI, 1.06-5.47; *P*=.036), even after adjustment for the metabolic syndrome.[2]

A study investigated the prevalence of myocardial infarction among patients with NASH compared with the general population.[3] Data were drawn from a large commercial database that provided electronic health records for more than 65 million patients from 26 major integrated US health care systems. The investigators searched the records for patients ages 18 years or older with a diagnosis of NASH made between 1999 to 2019, as well as for patients with a diagnosis of acute myocardial infarction made between 2018 and 2019. The study excluded patients with fatty liver, alcoholic hepatitis, or alcoholic fatty liver disease. To assess the correlation between myocardial infarction and risk factors, the investigators divided the entire cohort of patients into those with or without myocardial infarction. To calculate the prevalence of myocardial infarction within each risk group, they divided the number of patients with NASH within each group.

The study investigators identified 43,170 patients with NASH. After adjustment for comorbidities, NASH increased the risk of acute myocardial infarction by an OR of 1.5 (95% CI, 1.40-1.62; *P*<.0001). The relative risk of myocardial infarction was higher among younger patients than older patients (Figure 3). However, the absolute risk of myocardial infarction increased with age. Hyperlipidemia was the comorbidity that most strongly correlated with myocardial infarction (OR, 8.39; 95% CI, 8.21-8.58; *P*<.0001), followed by hypertension (OR, 3.11 (95% CI, 3.05-3.17; *P*<.0001), smoking (OR, 2.83; 95% CI, 2.79-2.87; *P*<.0001) diabetes mellitus (OR, 1.89; 95% CI, 1.86-1.91; *P*<.0001), obesity (OR, 1.78; 95% CI, 1.75-1.80; *P*<.0001), and male sex (OR, 1.53; 95% CI, 1.51-1.55; *P*<.0001). The OR was stronger for NASH than for older age (>65 years; OR, 1.47; 95% CI, 1.45-1.49; *P*<.0001).

The investigators concluded that NASH strongly correlated with myocardial infarction. Additional studies

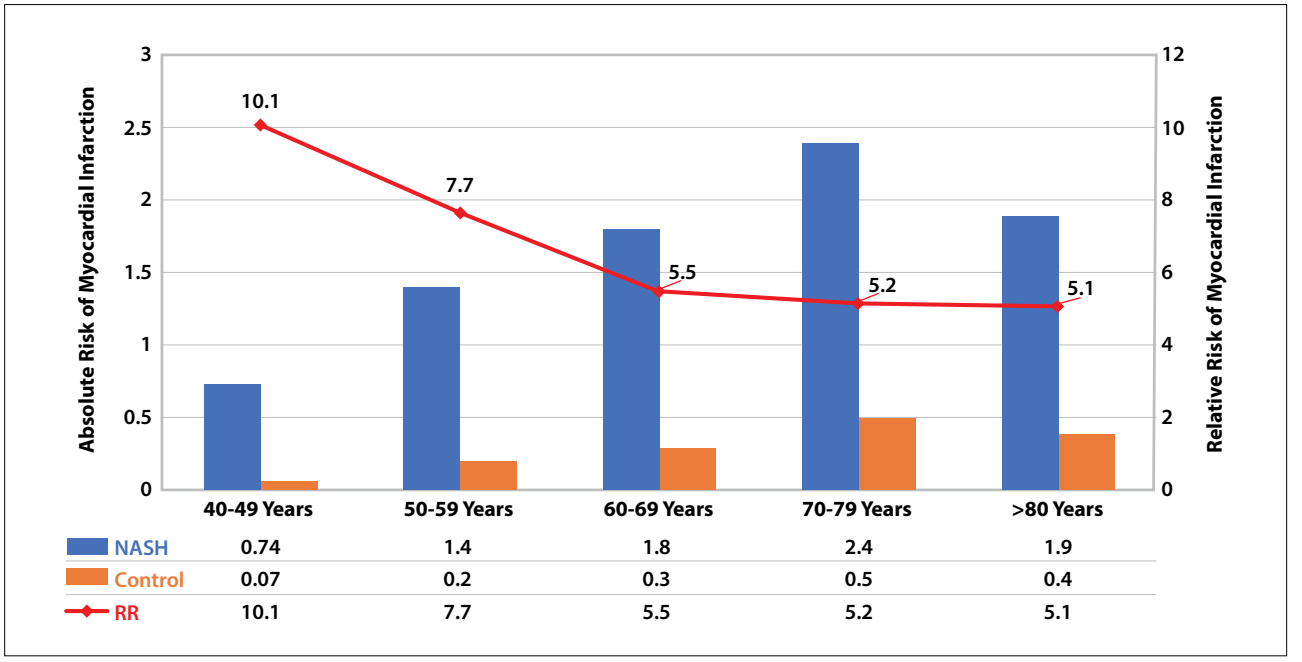

Figure 3. The risk of myocardial infarction according to age among patients with NASH. NASH, nonalcoholic steatohepatitis; RR, relative risk. Adapted from Ghoneim S et al. DDW abstract 234. *Gastroenterology.* 2020;158(6 suppl 1).[3]

are needed to provide further insight into the role of NASH in the pathogenesis of myocardial infarction. These data may lead to strategies to help prevent the progression of cardiovascular disease in patients with NASH.

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ABSTRACT SUMMARY Biochemical Effect of Obeticholic Acid in Non-alcoholic Steatohepatitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

A meta-analysis evaluated the biochemical response to obeticholic acid in adults with NASH (Abstract Tu1667). Three randomized controlled trials provided data for 500 patients: 248 in the obeticholic acid group and 252 in the placebo group. After 72 weeks of therapy, levels of alkaline phosphatase had increased by 16.3 IU/L more from baseline in patients treated with obeticholic acid compared with placebo (*P*=.0001). ALT levels decreased more in the obeticholic acid group compared with the placebo group (mean difference, 20.5 IU/L; *P*=.0001). Levels of AST and GGT also decreased more in the obeticholic acid group compared with placebo (AST, 11.9 IU/L; *P*=.007; GGT, 29.98 IU/L; *P*=.000). Changes in the total bilirubin level were similar for the 2 groups (*P*=.317).

Obesity-Specific Health-Related Quality of Life in Patients With Nonalcoholic Steatohepatitis: Results From the REGENERATE Study

Weight loss of 10% or more may reverse NASH and improve patients' health-related quality of life (HRQOL). However, only 3% to 6% of these patients are able to maintain such a weight loss.[1] An analysis of patients in the REGENERATE trial assessed the effect of obeticholic acid (10 mg or 25 mg) vs placebo on obesity-specific HRQOL.[2,3] The secondary objective was to determine the relationship between fibrosis/steatohepatitis and obesity-specific HRQOL. The study included 1218 patients in the expanded intention-to-treat population in the 18-month analysis of the trial.[4] Obesity-specific HRQOL was assessed in NASH patients without cirrhosis at baseline and at 6, 12, and 18 months, using the Impact of Weight on Quality of Life (IWQOL) questionnaire. The IWQOL questionnaire includes 5 domains: physical function, self-esteem, sexual life, public distress, and work. Each is evaluated on a scale of 0 to 100.

Patient characteristics were well-balanced among the 3 arms. The study population of 1218 patients had a mean age of 54.1 years, and 43.0% of patients were male. Fibrosis severity was categorized as stage 1 in 23%, stage 2 in 34%, and stage 3 in 43%. The mean BMI was 34.0 kg/m^2, the mean waist circumference was 111.5 cm, and the mean hip circumference was 114.9 cm.

At baseline, the mean IWQOL score was 83.3. The mean physical function score was 75.4, the mean self-esteem score was 74.4, and the mean sexual life score was 84.0. At month 18, the mean change in body weight from baseline was –2.17 kg with obeticholic acid at 25 mg, –1.78 kg with obeticholic acid at 10 mg, and –0.68 kg with placebo. The mean BMI changed by –0.78 kg/m^2, –0.63 kg/m^2, and –0.26 kg/m^2, respectively. The mean change in waist circumference compared with baseline was –1.69 cm

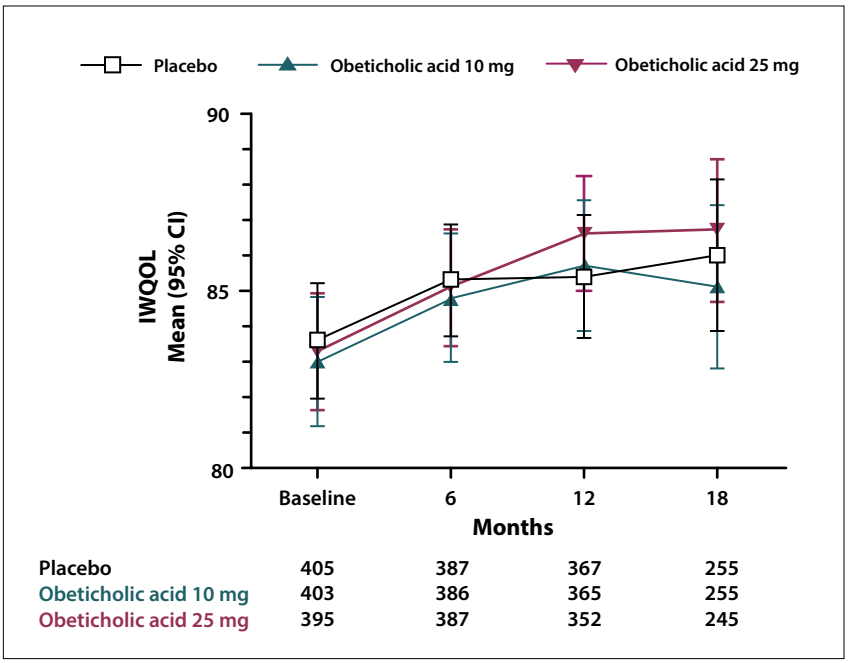

Figure 4. Changes in IWQOL scores over time among patients in the REGENERATE trial. IWQOL, Impact of Weight on Quality of Life. Adapted from Younossi ZM et al. DDW abstract 326. *Gastroenterology.* 2020;158(6 suppl 1).[3]

with the higher dose of obeticholic acid, –1.38 cm with the lower dose of obeticholic acid, and –1.23 cm with placebo. Mean change in hip circumference from baseline was –2.10 cm, –1.61 cm, and –1.44 cm, respectively.

From a mean baseline score of 83.3, the mean IWQOL score increased by 1.4 points at 6 months, 2.14 points at 12 months, and 2.12 points at 18 months (P<.01 for all time points; Figure 4). Improvement was comparable across the treatment groups over time (P>.05), with the exception of sexual life in the higher-dose obeticholic acid arm at month 18 (P<.02). In a pooled analysis of all patients who achieved the primary endpoint of fibrosis improvement by at least 1 stage with no worsening of NASH at month 18, the mean IWQOL score improved by 4.15 points as compared with 1.7 points among those who did not achieve the primary endpoint (P=.0341). Similarly, among the pooled group of patients who achieved the primary endpoint of NASH resolution with no worsening of fibrosis, the mean IWQOL score improved by 3.76 points vs 1.86 points among those who did not achieve this endpoint (P=.0742). At the end of the REGENERATE study, the investigators will evaluate the impact of weight loss and the dose-dependent effects of obeticholic acid on fibrosis and NASH.

ABSTRACT SUMMARY A Comprehensive Framework for Signal Assessment and Evaluation Following Anticipated Approval of the First Therapeutic in Patients With Non-Alcoholic Steatohepatitis

In anticipation of the approval of obeticholic acid, data sets are under development to enable the evaluation of safety signals in patients with NASH, by estimating background rates of various complications and comorbidities in NASH patients (Abstract Mo1481). Two cohorts of patients with NASH and no exposure to obeticholic acid were derived from 2 national databases. Clinical, demographic, and laboratory data were used to characterize patients and their disease severity. Following regulatory approval, a registry of NASH patients treated with obeticholic acid will be created. Approximately 100,000 patients were identified. The distribution of comorbidities was consistent with previous reports. For example, type 2 diabetes occurred in more than 40% of patients, dyslipidemia in more than 50%, and hypertension in more than 65%.

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Deleterious Impact of Advanced Nonalcoholic Steatohepatitis on Multiple Patient-Relevant Outcomes: An International, Cross-Sectional, Real-World Study

A real-world study evaluated the impact of liver fibrosis on the lives of patients with NASH.[1] Patient data were obtained from the 2018/2019 Adelphi NASH Disease Specific Programme, a cross-sectional survey conducted in the United States and the United Kingdom. Hepatologists, diabetologists, and gastroenterologists (in the United States and the United Kingdom), as well as primary care physicians (in the United States), completed questionnaires to characterize 5 consecutive patients with any-stage fibrosis, plus 2 additional patients with stage F3/F4 fibrosis. The patients were adults with NASH confirmed by either liver biopsy or noninvasive tests. Patients were retrospectively categorized with early or advanced fibrosis or as indeterminate based on published cutoff points. Assessments were based on the patient's most recent VCTE score, or by calculating the FIB-4.[2] The Child-Turcotte-Pugh score was used to identify patients with compensated cirrhosis or decompensated cirrhosis.[3] Patients completed a questionnaire to report on sleep, fatigue, work impairment, quality of life, and activities of daily living.

The study included 1245 patients with NASH seen by 162 physicians. Adequate self-reported data for analysis were available for 370 patients. One hundred ninety-five patients had undergone VCTE, 52 were categorized based on the FIB-4, and 123 were unassigned. VCTE and FIB-4 testing identified 157 patients with advanced fibrosis and 55 with early fibrosis. The mean age was 54.8 years in the group with advanced fibrosis and 48.7 years in the group with early fibrosis (P≤.001). More than half of patients (57%) were male, and the mean BMI was 34.0.

Rates of hypertension and dyslipidemia were similar for patients with advanced vs early fibrosis. However, patients with advanced fibrosis had higher rates of depression (18% vs 5%; P<.05) and anxiety (P<.05). Based on multivariate analyses, patients with advanced fibrosis reported a significantly higher impact on patient-relevant outcomes compared with patients with early fibrosis. Patients with advanced fibrosis reported a more severe impact on quality of life, based on results from both the EuroQol EQ-5D-5L (0.86

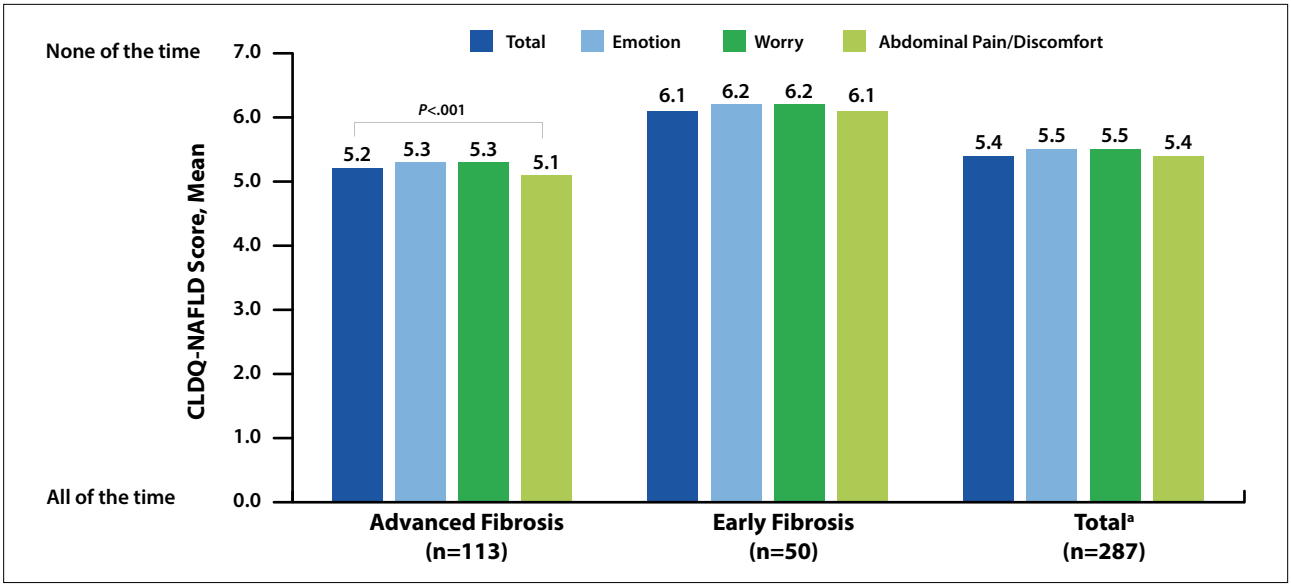

Figure 5. Patient-reported quality of life according to severity of fibrosis as assessed with the CLDQ-NAFLD. The *P* value was based on advanced fibrosis vs early fibrosis. [a]The total includes patients with advanced fibrosis, early fibrosis, indeterminate levels, and patients with missing vibration-controlled transient elastography or Fibrosis-4 Index values. CLDQ-NAFLD, Chronic Liver Disease Questionnaire–Non-Alcoholic Fatty Liver Disease. Adapted from Anstee QM et al. DDW abstract Mo1480. *Gastroenterology.* 2020;158(6 suppl 1).[1]

vs 0.93; *P*<.01) and the Chronic Liver Disease Questionnaire–Nonalcoholic Fatty Liver Disease (CLDQ-NAFLD; 5.2 vs 6.1; *P*<.001; Figure 5). Based on the anxiety and depression section of the EQ-5D-5L questionnaire, patients with advanced fibrosis reported a greater impact on psychologic well-being (1.7 vs 1.3; *P*<.01). The CLDQ-NAFLD questionnaire showed a greater impact on emotions (5.3 vs 6.2; *P*<.001) and worry (5.3 vs 6.2; *P*<.001) in patients with advanced fibrosis. Patients with advanced fibrosis were more likely to experience abdominal pain or discomfort, according to the EQ-5D-5L questionnaire (1.7 vs 1.4; *P*<.05) and the CLDQ-NAFLD questionnaire (5.1 vs 6.1; *P*<.001). Patients with advanced fibrosis reported greater sleep impairment (Jenkins Sleep Evaluation Questionnaire; 5.2 vs 2.0; *P*<.001) and more fatigue (CLDQ-NAFLD; 4.9 vs 5.8; *P*<.001). Patients with advanced fibrosis experienced a greater adverse impact on all activities of daily living, including freedom to eat and drink (1.5 vs 0.6; *P*<.001) and personal appearance/self-confidence (1.0 vs 0.2; *P*<.001). The Work Productivity and Impairment Questionnaire showed greater overall impairment regarding work (20.4% vs 12.0%) and significantly greater impairment experienced while working (19.2% vs 10.0%; *P*<.05) in patients with advanced fibrosis.

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Obeticholic Acid Improves Transaminases in Patients With Non-Alcoholic Steatohepatitis: Results From the 18-Month Interim Analysis of the REGENERATE Study

The 18-month interim analysis of the REGENERATE trial showed that obeticholic acid reversed fibrosis in patients with NASH and stage 2/3 fibrosis.[1] Levels of ALT and AST are often elevated in NASH patients, which may signal progression of fibrosis and other aspects of liver dysfunction.[2] An analysis of data from the REGENERATE trial evaluated whether improvement in transaminase levels in patients who received obeticholic acid could be used to monitor treatment response in NASH patients with fibrosis.[3] As part of the protocol-specified 18-month interim analysis, changes in ALT and AST were evaluated in the intention-to-treat population of 931 NASH patients with stage 2/3 fibrosis.

Patients treated with obeticholic acid at either dose experienced rapid, sustained, and dose-dependent reduction in levels of ALT and AST (Figure 6). These improvements were visible at month 1 and were sustained through month 18. Mean percentage reductions in ALT and AST levels were significantly improved in the active treatment arms compared with the placebo arm at all time points.

Among patients with levels of ALT that exceeded the upper limit of normal at baseline, these levels decreased

to below the upper limit of normal in 36% of the placebo arm, 49% of the 10-mg obeticholic acid arm, and 66% of the 25-mg obeticholic acid arm. The AST level was reduced to below the upper limit of normal in 28%, 42%, and 49% of patients, respectively. Among the cohort with ALT levels below the upper limit of normal at baseline, the proportion of patients whose levels increased beyond the upper limit of normal was 21% in the placebo arm, 9% in the 10-mg obeticholic acid arm, and 5% in the 25-mg obeticholic acid arm. For AST, these rates were 33%, 16%, and 15%, respectively. Among all patients treated with obeticholic acid, improvements in ALT and AST levels were greater in those who achieved the trial's primary endpoints compared with those who did not. However, improvements in transaminase levels at month 18 were observed among patients treated with obeticholic acid who did not achieve either of the primary endpoints.

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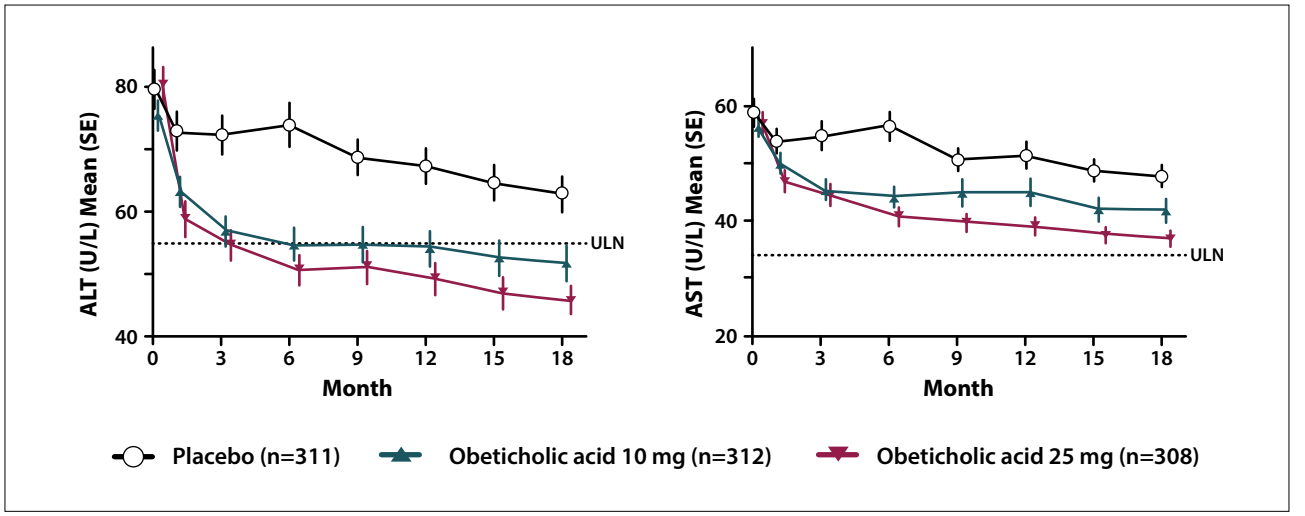

Figure 6. Changes in ALT and AST over time among patients in the intention-to-treat population of the REGENERATE trial. ALT, alanine transferase; AST, aspartate transferase; SE, standard error; ULN, upper limit of normal. Adapted from Rinella M et al. DDW abstract Mo1448. *Gastroenterology.* 2020;158(6 suppl 1).[3]

Identification of Significant Fibrosis in Patients With Nonalcoholic Steatohepatitis Using Noninvasive Tests: Determination of Optimal Thresholds Based on Cross-Sectional Analyses of Patients Screened for a Phase 3 Randomized Controlled Trial

NASH is characterized by accumulation of fat and inflammation of hepatocytes, with or without fibrosis.[1] Given the interest in therapies for patients with NASH and significant fibrosis, it is necessary to be able to identify such patients in real-world settings. Although liver biopsy is the gold standard for determining fibrosis stage, its use is limited in clinical practice, based on costs, complexity, and associated risks.[2] Researchers are evaluating noninvasive tests, including the FIB-4, APRI, and the NAFLD fibrosis score (NFS), for their ability to identify patients with advanced fibrosis.[3,4]

A retrospective study investigated noninvasive tests and optimal test thresholds to identify patients with significant fibrosis, using data from the phase 3 AURORA trial (Phase 3 Study for the Efficacy and Safety of CVC for the Treatment of Liver Fibrosis in Adults With NASH).[5] The AURORA study is investigating the efficacy and safety of cenicriviroc for the treatment of Clinical Research Network (CRN) stage 2/3 fibrosis associated with NASH. The current study included data from patients who underwent screening for the AURORA trial, some of whom did not meet the inclusion criteria. The database included 2056 patients with NASH, an evaluable screening liver biopsy, and results from

3 noninvasive tests: FIB-4, APRI, and NFS. Liver biopsies were read centrally to determine NASH CRN fibrosis stage, and the result from liver biopsy was used as the reference value. Patients were classified with either significant fibrosis (NASH CRN stage F2-F4) or nonsignificant fibrosis (NASH CRN stage F0-F1). The ability of each noninvasive test to identify the presence of significant fibrosis was evaluated by means of the receiver operating characteristic (ROC) curve. Tests were optimized for sensitivity and specificity, as well as classification accuracy. Minimal thresholds were 90% for specificity, to identify patients who were likely to have significant fibrosis, and 90% for sensitivity, to identify patients who were unlikely to have significant fibrosis.

Liver biopsy categorized 577 patients with stage F0 or F1 fibrosis and 1479 with stage F2, F3, or F4 fibrosis. At baseline, patients with stage F2 to F4 fibrosis had higher levels of ALT (60.5 vs 49.1 U/L), AST (48.1 vs 34.0 U/L), and gamma-glutamyl transferase (GGT; 73.1 vs 48.5 U/L).

The area under the ROC curve to identify significant fibrosis was acceptable for FIB-4 (0.71; 95% CI, 0.68-0.73; Figure 7) and APRI (0.69; 95% CI, 0.66-0.71), but not for NFS (0.62; 95% CI, 0.59-0.65). For the FIB-4 and APRI tests, Youden's Index failed to provide adequate sensitivity (65% and 63%, respectively) or specificity (68% and 64%, respectively). Based on the positive and negative predictive values obtained for each point on the FIB-4 and APRI ROC curves, no single cutoff point provided both optimal sensitivity (≥90%) and optimal specificity (≥90%). Based on a minimum threshold of 90% for both sensitivity and specificity, the thresholds selected for the 2 tests were 1.79 or higher for FIB-4 and 0.8 or higher for APRI to identify patients likely to have significant fibrosis. To identify patients who were unlikely to have significant fibrosis, cutoff values were 0.62 or lower for FIB-4 and 0.2 or lower for APRI.

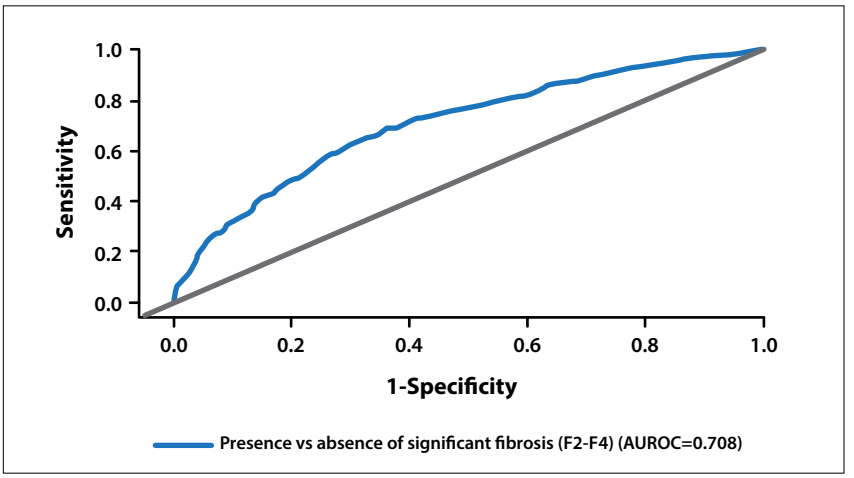

Figure 7. The FIB-4 receiver operating characteristic curve among patients screened for the AURORA trial. AUROC, area under receiver operating characteristic curve; FIB-4, Fibrosis-4 Index. Adapted from Shah D et al. DDW abstract Mo1445. *Gastroenterology.* 2020;158(6 suppl 1).[5]

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Obeticholic Acid Improves Hepatic Fibroinflammation as Assessed by Multiparametric MRI: Interim Results of the REGENERATE Trial

In the prespecified 18-month interim analysis of the phase 3 REGENERATE trial, improvement in fibrosis by at least 1 stage, based on liver biopsy, was observed in 23% of patients treated with obeticholic acid at 25 mg vs 12% of patients who received placebo (P=.0002).[1] Multiparametric magnetic resonance imaging (MRI) parameter T1 can be corrected for iron content (cT1) and used to quantify extracellular water content, which increases with levels of fibrosis and inflammation.[2-4] cT1 is a standard imaging biomarker of hepatic fibrosis and inflammation that has been shown to predict clinical outcomes.

Twenty patients enrolled in the REGENERATE trial were part of an exploratory evaluation of the effects of obeticholic acid on multiparametric MRI–derived cT1 mapping, which was used as a measure of inflammation and fibrosis.[5] Multiparametric scans were performed as an optional assessment at baseline and at months 6, 12, and 18. The analysis included 7 patients from the placebo arm, 6 from the 10-mg obeticholic acid arm, and 7 from the 25-mg obeticholic acid arm. At baseline, the mean cT1 was similar across the 3 treatment arms. Values in all 3 groups were in the elevated range—between 780 ms and 875 ms—consistent with the presence of

steatohepatitis and fibrosis. Fourteen patients (70%) had stage 3 fibrosis and 15 patients (75%) had a NAS of 6 or higher. The mean liver content at baseline was similar across the 3 groups, ranging from 15.3% (standard deviation, 7.3%) to 19.3% (standard deviation, 6.8%).

After 18 months of study treatment, a dose-dependent reduction in cT1 was observed (Figure 8). The mean change from baseline was –1.4 ms in the placebo group, –59.6 ms in the 10-mg obeticholic acid group, and –91.7 ms in the 25-mg obeticholic acid group. Reductions were observed at all 3 time points. Although the lower dose of obeticholic acid did not appear to affect liver fat content, the higher dose yielded a liver fat content reduction of –7.9%, with the change again observed as early as month 6 and generally sustained through month 18. The mean change in NAS with standard error (SE) was –0.4 (SE, 0.53) for patients in the placebo arm, –1.5 (SE, 0.56) for those in the 10-mg obeticholic acid arm, and –2.5 (SE, 1.44) for those in 25-mg obeticholic acid arm. The mean change in ALT was –21.0 (SE, 10.4), –12.1 (SE, 12.7), and –109.1 (SE, 62.9), respectively. These findings were consistent with the results observed from liver biopsy.

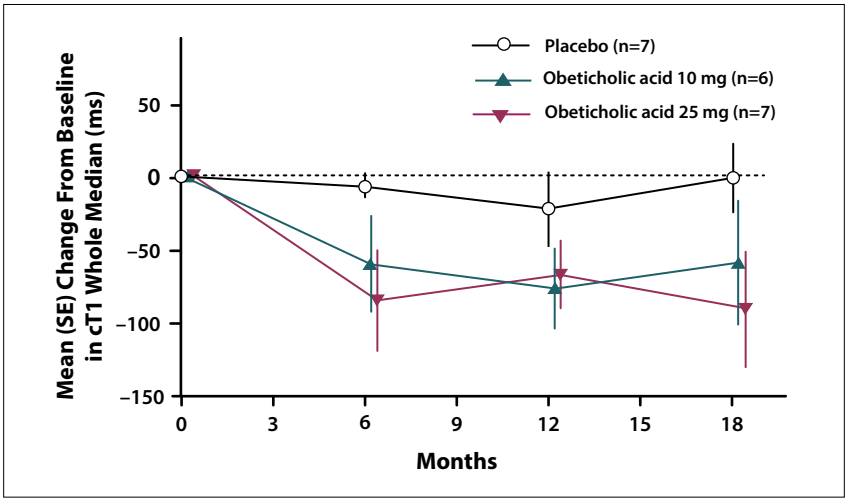

Figure 8. Changes in median cT1 levels among 20 patients from the REGENERATE study who were part of an exploratory evaluation. cT1, T1 corrected for iron content; SE, standard error. Adapted from Loomba R et al. DDW abstract Tu1665. *Gastroenterology.* 2020;158(6 suppl 1).[5]

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Long-Term Safety Profile of Cenicriviroc in Adults With Nonalcoholic Steatohepatitis: Rollover Study

Cenicriviroc is a potent, oral antagonist of the C-C chemokine receptor types 2 and 5. In the phase 2b CENTAUR study (Efficacy and Safety Study of Cenicriviroc for the Treatment of Nonalcoholic Steatohepatitis [NASH] in Adult Participants With Liver Fibrosis), cenicriviroc demonstrated a significant reduction in the biomarkers associated with progression of fibrosis over 2 years vs placebo.[1,2] The CENTAUR Rollover study included patients who completed 2 years of treatment in the CENTAUR study, plus patients who met prespecified, adjudicated events in the phase 3 AURORA study.[3] These patients are part of a long-term safety evaluation of cenicriviroc. Patients who had completed the CENTAUR study were included in an interim analysis. Safety endpoints were collected every 3 months and included clinical laboratory assessments, adverse events (AEs), AE severity, and assessments by the investigator of whether the AE was related to treatment.

Among the 106 patients who had rolled over from CENTAUR, the mean age was 57.4 years. Fibrosis stage 1, 2, or 3 was observed in 34.0%, 29.2%, and 37.8% of patients, respectively. Patients from CENTAUR were treated with cenicriviroc for a mean of 1176.8 days (standard deviation, 249.8), or 341.5 participant-years. The duration of treatment with cenicriviroc ranged from 36 to 48 months for 46.2% of patients (Figure 9). Across the entire study group, 79.2% experienced an AE of any grade. Treatment-related AEs were absent among patients who received cenicriviroc for less than 24 months. They were observed in 6.7% of patients who were treated for more than 48 months, in 10.2% of patients treated between 36 and less than 48 months, and in 13.9% of patients treated for at least 24 months and less than 36 months. Only 1 grade 3 AE, an increase in total bilirubin, was considered related to study drug treatment by the investigator. This AE occurred in a patient with a history of Gilbert syndrome. One patient developed several grade 4 AEs and was hospitalized with acute kidney injury, uremic

encephalopathy, and gastroenteritis. None of these events were considered related to the study treatment. One patient discontinued cenicriviroc after developing elevated levels of ALT and AST. The elevations were considered unrelated to study drug treatment.

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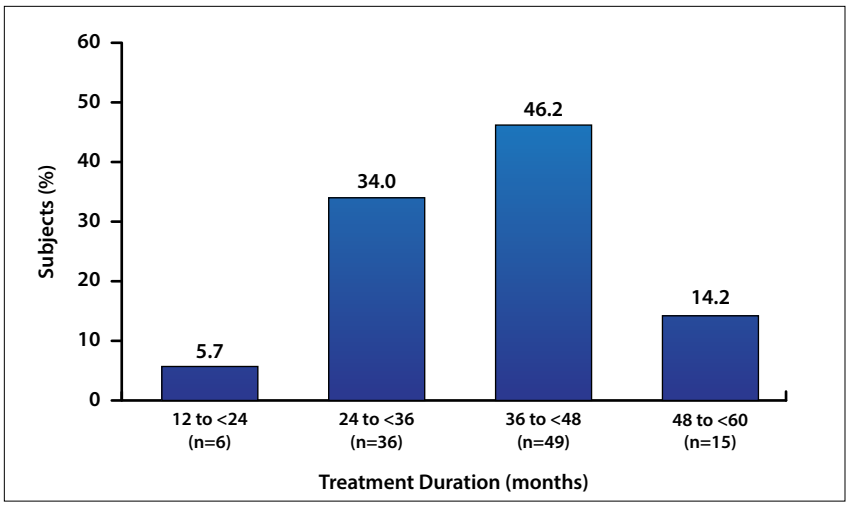

Figure 9. Duration of treatment with cenicriviroc among patients in the CENTAUR trial. Adapted from Francque S et al. DDW abstract Tu1673. *Gastroenterology.* 2020;158(6 suppl 1).[3]

Highlights in Nonalcoholic Steatohepatitis (NASH) From Digestive Disease Week 2020: Commentary

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Digestive Disease Week 2020 was presented in a virtual format. Many abstracts provided important data on the management of patients diagnosed with nonalcoholic steatohepatitis (NASH). Studies focused on the association between NASH and myocardial infarction, further post-hoc analyses of the phase 3 trial data for obeticholic acid, the use of noninvasive tests, and the impact of advanced NASH on patient outcomes.

NASH and Myocardial Infarction

Dr Sara Ghoneim and colleagues presented results from a meta-analysis examining the important topic of the prevalence of myocardial infarction among patients with NASH.[1] Nonalcoholic fatty liver disease (NAFLD) is associated with increased liver-related morbidity and mortality.[2] However, the more common cause of increased mortality among these patients is cardiovascular disease.[3] Researchers are evaluating the mechanisms underlying myocardial infarction in these patients, as well as the frequency and most common settings.[4,5] Studies aim to determine whether the rates of myocardial infarction are increased among all patients with fatty liver, or limited to subsets such as those with advanced fatty liver disease or NASH and advanced fibrosis.

A previous meta-analysis of more than 34,000 subjects found that patients with more severe NAFLD were at increased risk of developing nonfatal and fatal cardiovascular events, with a strong odds ratio of 2.58.[6] In a prospective observational study of nearly 900 patients, fatty liver disease increased the risk for cardiovascular events, with a hazard ratio of 2.41 (even after adjusting for metabolic syndrome).[7]

The meta-analysis by Dr Ghoneim included more than 43,000 patients with NASH.[1] This national population-based study aimed to assess the prevalence of acute myocardial infarction among patients with NASH and to investigate the contribution of age and sex on the relative risk of myocardial infarction in a large cohort of subjects. The investigators evaluated a database that contains patient information from 26 major integrated health care systems throughout the 50 states, providing approximately 55 million unique patient records. They

identified patients with NASH and a diagnosis of acute myocardial infarction (according to standard SNOMED CT terminology) from 1999 to 2019, with the goal of establishing a temporal relationship. Patients were excluded from the analysis if they had alcoholic hepatitis, alcoholic fatty liver disease, or simply fatty liver.

The key finding of the analysis was that NASH is associated with acute myocardial infarction, independent of traditional risk factors. In addition, the relative risk for acute myocardial infarction was higher in younger patients vs older patients. Premenopausal women with NASH had a higher relative risk of myocardial infarction compared with postmenopausal women. This finding may be partially explained by the younger patients' lower cardiovascular disease risk profile at baseline as compared with their older counterparts.

Limitations to the study included the cross-sectional design, which always precludes conclusions regarding causality. Databases are prone to coding errors. It is difficult to establish direct temporal relationships between the duration of NASH, the severity of the disease, and the impact of interventions on the risk of cardiovascular outcomes.

Obeticholic Acid

Obeticholic acid is a potent farnesoid X nuclear receptor agonist.[8] Dr Jérôme Boursier and colleagues examined the impact of obeticholic acid on experimental noninvasive markers of NASH.[9] Data were drawn, post hoc, from the month-18 interim analysis of the phase 3 REGENERATE trial (Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment), which is comparing obeticholic acid vs placebo among patients with NASH and fibrosis.[10] The REGENERATE trial randomly assigned patients with fibrosis of F1 (plus a comorbidity), F2, or F3 severity in a 1:1:1 manner to placebo, obeticholic acid at 10 mg/day, or obeticholic acid at 25 mg/day. The month-18 interim analysis was conducted among patients with fibrosis of F2 or F3 in the intention-to-treat population.[10] This analysis showed that treatment with obeticholic acid improved liver fibrosis and established noninvasive assessments of fibrosis among patients with F2 or F3 fibrosis.

There are new biomarker indices in development to improve the ability to predict NASH and fibrosis in a noninvasive manner. The analysis by Dr Boursier evaluated 3 of these noninvasive tests.[9] FibroMeter was designed to predict the presence of significant fibrosis, meaning F2 or higher.[11] This test combines age, sex, alpha-2 macroglobulin, international normalized ratio, platelets, urea, and gamma-glutamyl transferase. FibroMeter VCTE uses the same biomarkers, except urea, and adds liver stiffness as measured by vibration-controlled transient elastography (VCTE).[12] The FibroScan-AST (FAST) score was designed to identify patients with NASH who have an NAFLD activity score of 4 or higher and fibrosis severity of F2 or worse.[13] This score combines liver stiffness as measured by VCTE with the controlled attenuation parameter (CAP), as well as levels of the serum biomarker aspartate transaminase (AST).

In a subset of patients with available values, changes in FibroMeter, FibroMeter VCTE, and FAST were analyzed using a mixed-effect repeated measures model, which provided least square mean values and *P* values.[9] At baseline, there were no significant differences in scores across the treatment groups. Patients with stage 3 fibrosis at baseline had higher noninvasive markers than those with stage 2 fibrosis at baseline. Among patients treated with obeticholic acid, FibroMeter, FibroMeter VCTE, and FAST scores improved at the first assessment time point at month 6, and these improvements were sustained through month 18. This therapeutic response was observed in both obeticholic acid groups, but not in the placebo group.

According to this analysis, treatment with obeticholic acid resulted in early and sustained improvement in results from experimental noninvasive tests evaluating severity of fibrosis in NASH. More specifically, improvements in FibroMeter and FibroMeter VCTE were consistent with the antifibrotic effect of obeticholic acid, and improvements in FAST were consistent with amelioration of key histologic features of NASH, including inflammation and fibrosis.

This analysis provides important data supporting the use of noninvasive tests. Clinicians are aiming to identify noninvasive tests that address 3 key contexts of use. The first application is for the diagnosis of NASH patients with fibrosis, particularly F2 or F3. The second is to identify markers of therapeutic efficacy. The third is to measure long-term outcome. FibroMeter, FibroMeter VCTE, and FAST are tied to histology, which is the gold standard—albeit an imperfect one—that provides the comparator for noninvasive testing. These data are important as investigators begin to build the case for regulatory authorities, payers, and clinicians to move away from liver biopsy and toward noninvasive testing.

Dr Zobair Younossi and colleagues provided an analysis of the 18-month REGENERATE data that focused on obesity-specific health-related quality of life.[14] NASH patients are typically overweight or obese, which can negatively impact health-related quality of life. Weight loss may reverse NASH, and may also improve health-related quality-of-life outcomes.[15] The aim of this analysis was to determine whether the improvements in fibrosis seen with obeticholic acid corresponded to improvements in obesity-specific health-related quality of life.

The investigators assessed obesity-specific health-related quality of life at 4 different time points—baseline, 6 months, 12 months, and 18 months—through the Impact of Weight on Quality of Life (IWQOL), a validated self-reported questionnaire. The questionnaire includes 5 domains: physical function, self-esteem, sexual life, public distress, and work. The scores are averaged to calculate the total impact

of weight on quality of life.

Compared with placebo, treatment with obeticholic acid at 10 mg or 25 mg was associated with a higher mean reduction in weight and body mass index from baseline to month 18. The mean total impact of weight on quality-of-life scores showed a significant increase at month 6, month 12, and month 18 compared with baseline. These increases were driven by improvements in physical function, self-esteem, and sexual life. Improvement was comparable across treatment groups in fibrosis stages over time, except for sexual life in obeticholic acid at 25 mg at month 18 (P<.02).

In the REGENERATE study, patients who met the endpoints at month 18 experienced a greater mean impact of weight on quality-of-life improvement.[10] The change in IWQOL scores was 4.15 among patients with improvement in fibrosis compared with 1.7 among those who did not achieve this endpoint. Among patients who achieved NASH resolution with no worsening of fibrosis, the change in IWQOL scores was 3.76 vs 1.86 in those who did not reach this endpoint. In conclusion, measurement of the impact of weight on quality of life showed impairment at baseline that improved in a dose-dependent manner across the treatment groups.

Dr Mohammad Alomari and colleagues presented a systematic review and meta-analysis evaluating the biochemical effects of obeticholic acid in NASH.[16] Clinical trial data have established that obeticholic acid leads to a significant reduction in liver enzymes and liver fibrosis, with a strong correlation to improved outcomes in patients with NASH.[10] However, there has been substantial variation in the reported pattern of liver enzyme alteration among these trials. Therefore, the overall effect of obeticholic acid on liver enzymes is unclear.

The meta-analysis included randomized, controlled trials that compared obeticholic acid vs placebo in patients with NASH.[16] A thorough search was performed on multiple different databases, such as PubMed, Medline, Google Scholar, and the Cochrane database, from inception through November 2019. Eligible studies were examined for variables of interest, including change in alkaline phosphatase, alanine aminotransferase (ALT), AST, gamma-glutamyl transferase, and total bilirubin from baseline. Publication bias was addressed with conventional techniques. Pooled standardized mean differences were reported with a 95% confidence interval.

Five hundred patients from 3 randomized, controlled trials were available for the qualitative synthesis of the meta-analysis.[16] There were 248 patients in the obeticholic acid group and 252 patients in the placebo group. After 18 months of therapy, increases in the level of alkaline phosphatase from baseline were higher among patients treated with obeticholic acid vs placebo, for a mean difference of approximately 16.3 IU/L (P=.0001). The reduction in ALT levels was greater in patients treated with obeticholic acid vs placebo, for a mean difference of 20.5 IU/L (P=.0001). Similarly, AST and gamma-glutamyl transferase levels were decreased with obeticholic acid vs placebo. The mean differences were 11.9 IU/L for AST and 29.98 IU/L for gamma-glutamyl transferase.

In conclusion, obeticholic acid administered at a dose of 25 mg/day for 72 weeks reduced nearly all liver enzymes in patients with fibrosis due to NASH. The one exception was alkaline phosphatase. Most of the patients in this analysis had a normal level of alkaline phosphatase at the time of enrollment, for a pooled mean value of 81 ± 25 IU/L. The investigators suggested that the mild increase in levels of alkaline phosphatase observed with obeticholic acid are of limited clinical relevance. This is likely because alkaline phosphatase elevation is a consequence of an on-target effect of farnesoid X receptor activation. Based on personal discussions with researchers at Intercept Pharmaceuticals, the manufacturer of obeticholic acid, unpublished data show that phospholipase D is elevated in the setting of obeticholic acid therapy, and this enzyme is responsible for the cleavage of alkaline phosphatase from its anchor protein and thus the increase in soluble protein observed in serum.

The Accuracy of Noninvasive Tests

Dr Darshini Shah and colleagues provided an analysis of the accuracy of noninvasive tests used to screen patients for enrollment in the phase 3 AURORA trial (Phase 3 Study for the Efficacy and Safety of Cenicriviroc [CVC] for the Treatment of Liver Fibrosis in Adults With NASH).[17] The objectives of the study were to evaluate the accuracy of noninvasive tests in discriminating significant fibrosis and to determine the optimal thresholds for identification of significant fibrosis. The AURORA trial is currently enrolling patients to evaluate the efficacy and safety of cenicriviroc for the treatment of NASH and fibrosis, specifically F2 and F3 fibrosis.[18] Laboratory tests and noninvasive tests were performed as part of the screening process. Subjects underwent liver biopsy to confirm histologic evidence of NASH and fibrosis stages F2 and F3.

The investigators analyzed data from an interim data cut of the AURORA screening database.[17] The analysis included subjects who underwent screening for the trial, regardless of whether they met the inclusion criteria. Using liver biopsy as the gold-standard reference, subjects were categorized with either significant NASH (defined as F2 to F4 disease) or nonsignificant NASH (defined as F0 to F1 disease). The ability of each noninvasive test to discriminate significant fibrosis was evaluated using receiver operating characteristic curves.

Three noninvasive tests were used: FIB-4, the AST to Platelet Ratio Index (APRI), and the NAFLD fibrosis score. According to a receiver operating characteristic analysis, a FIB-4 cut point of 1.13 identified significant fibrosis with a sensitivity of 65%, a specificity of 68%, a negative predictive value of

43%, and a positive predictive value of 84%. With an APRI cut point of 0.44, these values were 63%, 64%, 40%, and 82%, respectively.

FIB-4 and APRI cutoffs and related measures for subjects likely or unlikely to have significant fibrosis were evaluated. In this analysis, the FIB-4 cut point was 1.79. The sensitivity was low, at 31%. The specificity, however, was 91%, driving a positive predictive value of 90% and a negative predictive value of 34%. For APRI, with a cut point of 0.8, the sensitivity was low, at 27%. However, the specificity was 92%, leading to a positive predictive value of 90% and a low negative predictive value of 33%.

Ultimately, 2 thresholds were selected to maximize classification accuracy: a high threshold above which subjects were likely to have significant fibrosis optimized for specificity greater than 90%, and a low threshold below which subjects were unlikely to have significant fibrosis. The study results are reflective of the current status of these data points in the field. The positive or negative predictive value will significantly change based on the patient population screened. Use of the cut points that are defined in this analysis can allow a very high positive predictive value because they are selecting patients most likely to have advanced liver disease. This finding is applicable to clinics with a population consisting mainly of patients with advanced fibrosis. Applying these cut points to the general population, particularly in a primary care environment, would lead to very different positive predictive values because the prevalence of underlying advanced disease would be much lower.

The Impact of Advanced NASH on Patient Outcomes

Dr Quentin Anstee and coworkers presented data from an international, cross-sectional, real-world study that evaluated the impact of advanced NASH on patient outcomes.[19] NASH is often described as asymptomatic, but patients with advanced fibrosis—meaning F3 or higher—are at higher risk for developing adverse health outcomes vs patients with earlier-stage disease.[20] It is known that NASH patients have decreased health-related quality of life and impaired work productivity compared with the general population.[21] However, data are limited concerning the impact of the NASH fibrosis stage on a wider range of patient-related outcomes. The objective of this trial was to evaluate the impact of advanced fibrosis on patients' lives by comparing multiple outcomes among those with advanced fibrosis vs early fibrosis (as identified with published cutoffs for noninvasive tests).

The data were derived from the 2018/2019 Adelphi NASH disease-specific outcome program, a cross-sectional survey conducted in the United States and the United Kingdom.[22-24] Hepatologists, gastroenterologists, diabetologists, and primary care physicians completed questionnaires describing 5 consecutive NASH patients and a further 2 patients with F3 and F4 disease. The analysis included patients ages 18 years and older with NASH (confirmed by a liver biopsy or a noninvasive test), who were not currently enrolled in a clinical trial.

The patients were retrospectively categorized with advanced fibrosis, early fibrosis, or as indeterminate according to published cut points. Assessment was based on the most recent VCTE results. When VCTE was not conducted, a FIB-4 test was calculated. Child-Turcotte-Pugh scores identified patients with compensated cirrhosis and decompensated cirrhosis. A patient-reported questionnaire captured several different variables, drawing from the Jenkins Sleep Evaluation Questionnaire, the Chronic Liver Disease Questionnaire, and others.

The take-home point from this real-world study is that patients with NASH and advanced fibrosis reported significant impairment across a range of self-reported outcomes vs patients with early fibrosis. Anxiety and depression are more common among patients with advanced fibrosis. In addition, patients with advanced fibrosis experience significantly greater burdens related to their psychology, well-being, sleep, and, importantly, work. Historically, NASH had been considered an asymptomatic disease.[25] This analysis, however, contradicts that dogma and highlights the correlation between fibrosis severity and patient burden over time.

Use of the FAST Score to Identify At-Risk Patients

Dr Brittany Mitchell and colleagues provided results from a study that evaluated the validity and use of the FAST score in identifying at-risk NAFLD patients.[26] With noninvasive tests, combination sequential testing provides better positive predictive value than a single test, whether a wet biomarker or an imaging biomarker. Data for the FAST test were recently published in *The Lancet Gastroenterology and Hepatology*.[13] FAST combines sequential testing of AST, a serum laboratory biomarker, with the imaging procedure VCTE. This study was performed at the Cleveland Clinic. The investigators searched electronic medical records using institutional procedural codes for FibroScan and liver biopsy, and they manually reviewed the charts for data extraction. Data were gathered from 2017 to 2018. The study included patients with biopsy-confirmed NAFLD who underwent a liver biopsy and a FibroScan within 6 months of each other.

The study defined at-risk NASH as a NAFLD Activity Score (NAS) of 4 or higher and a biopsy fibrosis score of 2 or higher. The study used a FAST score cutoff of less than 0.35 to indicate that a patient was unlikely to have at-risk NASH. A value higher than 0.67 was likely to rule in at-risk NASH.

The study evaluated 2 separate methods of analysis. The first method excluded patients with an indeterminate FAST score (0.35-0.67), who amounted to 44% of the cohort (n=56). The second analytic method

included patients with an indeterminate score. For these patients, the investigators postulated that the FAST score led to an inaccurate categorization. The patients were counted toward the false-positive or false-negative total based on their biopsy results. There were 100 of these patients.

Among the 56 patients assessed with the first method, FAST results were concordant between biopsy and the NAS and the fibrosis score in 37 and discordant for 19. The overall accuracy of FAST to identify at-risk fibrotic NASH was 66%. Among the 19 patients with discordant results, all were false positives. Use of this method led to a sensitivity of 100%, a specificity of 58%, a positive predictive value of 37%, and a negative predictive value of 100%.

With the second method, results for 38 out of 100 patients were concordant between the biopsy and the NAS and the fibrosis score. The remaining 62 patients were discordant. Among these patients, 8 were false negatives and 54 were false positives. Overall, the accuracy of FAST was only 37%, with a sensitivity of 60%, a specificity of 32%, a positive predictive value of 18%, and a negative predictive value of 74%.

This study suggests that the FAST score may have strong sensitivity and a strong negative predictive value. When excluding indeterminate results and using the calculator as recommended, the sensitivity was 100% and the negative predictive value was 100%. These results provide further data regarding the use of FAST as a noninvasive methodology for identifying at-risk patients with NASH. Further evaluation is needed in multiple data sets, such as this one, to determine the validity and proper application of this risk calculator.

Disclosures

Dr Harrison is an advisory board member and/or a consultant of Akero, Altimmune, Arrowhead, Axcella, Cirius, CiVi Biopharma, CLDF, Cymabay, Echosens, Foresite Labs, Fortress, Galectin, Gelesis, Genfit, Gilead, Hepion, HighTide Bio, HistoIndex, Intercept, Kowa, Madrigal, Medpace, Metacrine, NGM Bio, NorthSea, Novartis, Novo Nordisk, Poxel, Prometic, Ridgeline Therapeutics, Sagimet, Terns, and Viking. He has received grant/research support from Axcella, BMS, Cirius, CiVi Biopharma, Conatus, Cymabay, Enyo, Galectin, Galmed, Genentech, Genfit, Gilead, Hepion, HighTide Bio, Immuron, Intercept, Madrigal, NGM Bio, NorthSea, Novartis, Novo Nordisk, Pfizer, Sagimet, Second Genome, Tobira/Allergan, and Viking. He owns stock/shares (self-managed) in Akero, Cirius, Galectin, Genfit, Hepion, HistoIndex, Metacrine, NGM Bio, and NorthSea.

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