Abstract #969

AASLD Presidential Poster of Distinction

Outcome in SVR HCV patients

HCV

Long-Term Follow Up of Patients with Chronic HCV and No or Minimal Fibrosis Shows Low Risk for Liver-Related Morbidity and Mortality After Achieving SVR with DAA-Based Therapy: Results from the Gilead SVR Registry

M Bourlière, EJ. Gane, I Jacobson, SC Gordon, MS Sulkowski, BL McNabb, F Chen, H Dvory-Sobol, J McNally, DM Brainard, M Subramanian, A Ramji, S Zeuzem, K Agarwa, KR Reddy

Background: HCV-infected patients with minimal fibrosis have a lower risk for liver-related clinical events. Little is known about longer term outcomes after achieving SVR with direct-acting antiviral (DAA) therapy. Here we describe the incidence of liver related morbidity and mortality among patients with F0-F1 fibrosis who have achieved SVR from DAA-based therapy. **Methods**: Patients were enrolled in the Gilead SVR Registry ≤ 3 months after achieving SVR with at least one DAA. Visits occurred ever 24 weeks for up to 144 weeks. Patients with F0-F1 fibrosis (FibroTest 0-0.21 measured prior to DAA-regimen) were included. Assessment for signs of jaundice, ascites, hepatic encephalopathy (HE), varices, and hepatocellular carcinoma (HCC) and measurement of albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelets (PLT), prothrombin time (PT), and total bilirubin (Bili) occurred at each visit. **Results**: A total of 1393 (632 [45%] on study, 482 [35%] completed study, and 279 [20%] discontinued study]) patients with fibrosis scores F0-F1 were enrolled, with median (range) registry follow up time of 2.5 (0.6-4.3) years. Of these, 40% were male, 86% were white, and the mean (range) age was 47 (19-79) years. The DAA-regimen was sofosbuvir (SOF)+ribavirin (RBV)±pegylated interferon (PEG) for 21%, ledipasvir (LDV)/SOF±RBV for 32%, SOF/velpatasvir (VEL) ±RBV for 31%, SOF/VEL/voxilaprevir (VOX) for 13%, and other for 3% of patients. No HCC was reported in any patient with 3468 person-years of follow up. There was 1 (0.1%) event of jaundice at week 48, 1 (0.1%) event of ascites atweek 72, 1 (0.2%) event of HE at week 120, and 0 events of varices. Mean week 144 ALB, ALT, AST, PLT, PT, and Bili were all within normal limits and comparable to baseline values. Six patients died during the observation period, with no causes of death due to liver disease. There were 8 patients with virologic failure (6 reinfections, 1 relapse, and 1 investigation ongoing). **Conclusions**: In HCV-infected patients with minimal fibrosis who achieve SVR with DAA therapy, rates of liver-related complications, liver-related laboratory abnormalities, HCV relapse, and death are very rare in the first 144 weeks of follow-up. These data support early treatment of HCV infection and may be useful in guiding monitoring strategies for HCC and other liver-related events following SVR.

Abstract #998

Outcome in SVR HCV patients

HCV

Impact of HCV treatment on long term mortality in patients ≥70 years at the time of HCV infection diagnosis

C Legué, C Jezequel, C Pronier, A Rabot, P Houssel-Debry, L Legros, T Uguen , C Le Lan, R Moirand, E Bardou-Jacquet, B Turlin, V Thibault, D Guyader

Direct antiviral agents (DAA) allow efficient treatment of HCV infection, decreasing hepatic and extrahepatic mortality. The impact of treatment on long term survival in elderly patients, especially in case of non severe F0-2 fibrosis, is however difficult to assess. **The aim** of the study was to define long term prognosis (overall, liver related and non liver related mortality) of the treatment in a cohort of patients who had age ≥ 70 years at inclusion. **Methods** : Patients were selected from a cohort of consecutive HCV positive patients. Significant data were extracted. Survival and causes of death were obtained from national registry of death certificate. Liver fibrosis was determined using liver biopsy or non invasive tests (elastography or FibroTest.). Survival curves were constructed with T0 at inclusion. **Results** : 280/4416 patients had ≥ 70 years at inclusion ; 244/280 were HCV-RNA positive and included in the study. Median age was 73 [IQR 71-77] ranging from 70 to 91 years ; women = 42.9% ; 74.8% infected by genotype 1. Stage of fibrosis at inclusion was F0/F1 in 33.9%, F2 in 12.1%, F3 in 15.5% and F4 in 27.6%. 91/244 patients have been treated (mainly using interferon/ ribavirin) and 32/91 (35.2%) reached sustained virological response (SVR). Mean duration of follow-up as 11.7 years [6.4-19.8]. 134/244 patients (54.9%) died. Death was liver related in 73 cases (61.9%), comprising 29 cases of hepatocellular carcinoma, and non liver related in 45 cases (38.1%). Overall survival of the cohort was 96.7%, 77.7%, 58.3% and 36.6% at 1, 5, 10, 15 years. There was no survival benefit of treatment nor SVR which contrasted with the clear benefit (p<0.0001) demonstrated in younger patients of the cohort. The graph shows results in the F0-2 subgroup. **Conclusion** : The impact of the treatment on survival decreases with age. Early therapy is important.

Abstract #982

Outcome in SVR HCV patients

HCV

Liver disease monitoring after hepatitis C cure in underserved patients with advanced liver fibrosis

NJ Kim, M Khalili

Background There is limited guidance on monitoring of HCV-infected patients who achieve a sustained virologic response 12 weeks (SVR12) post direct acting antiviral therapy (DAA) and real world data on practice patterns in this setting is lacking. However, continued screening for hepatocellular carcinoma (HCC) in those with advanced fibrosis pre-therapy is recommended. **We aimed** to characterize real world liver disease monitoring and HCC screening practice patterns after achieving SVR12 in a cohort of underserved HCV-infected patients. **Methods** Records of 170 HCV-infected patients who initiated DAA therapy at the San Francisco safety-net healthcare system's liver specialty clinic between January 2014 and January 2016, who achieved SVR12 and had ≥12 months of follow-up post-SVR12 were reviewed with respect to demographics and clinical data. Liver disease monitoring was defined as liver clinic visits, laboratory evaluation, and liver imaging studies. Advanced fibrosis pre-therapy was defined as F3 or F4 based on liver biopsy (33%), FibroTest (9%), or clinical and imaging studies confirming cirrhosis. **Results** Characteristics of patients (73% genotype 1, 21% genotype 2/3, 6% other genotype) with SVR12 were: median post-SVR12 follow-up of 19 (range 12-34) months, median age 58.5, 61% male, 42% White (23% Black, 15% Latino, 20% Other), 78% English-proficient, 36% with prior psychiatric history, 49% prior IVDU, 38% prior (15% current) alcohol use, 41% advance fibrosis (34% with cirrhosis of whom 33% had decompensation, 16% HCC). During post-SVR12 follow-up, a higher proportion of patients with advanced fibrosis attended liver clinic visits (mean 1.8±1.9 vs 1.2±1 visits, p=0.004) and had ≥2 liver imaging (45% vs 5%, p<0.0001) but not ≥2 ALT evaluations (71% vs 66%, p=0.5) compared to those without advanced fibrosis. However, 25% of those with advanced fibrosis had no liver clinic visits, 25% had no liver imaging, and 8% had no ALT evaluation post SVR12 while 3% had ≥5 liver imaging and 28% had ≥5 ALT evaluations. Post-SVR12 68% had SVR24 or SVR48 evaluation and three cirrhotic patients developed new HCC. **Conclusions** In this underserved cohort of patients with HCV cure, majority of patients with advanced fibrosis underwent both disease monitoring and HCC screening following SVR12 and new cases of HCC were identified even within a short period. However, 25% did not have a liver clinic visit or imaging study. With HCV treatment extension into non-specialty settings, enhanced guidelines along with patient and provider education are critical to optimize post-SVR monitoring in those with advanced fibrosis, especially in difficult to engage populations.

Abstract #1002

Fibrosis monitoring after SVR

HCV

Prospective assessment of the impact of successful DAAs treatment on liver fibrosis stage and predictors of fibrosis regression in patients with chronic hepatitis C and advanced fibrosis stage

Y Davidov, Y Kleinbaum, Y Inbar, O Cohen-Ezra, E Veitsman, P Weiss, S Katsherginsky, K Tsaraf, Z Ben-Ari

Background: The new direct-acting antiviral agent (DAAs) therapies have demonstrated a high sustained virological response rate (SVR) in patients with hepatitis C virus infection (HCV) however the impact of SVR on fibrosis stage was not evaluated. We have prospectively explored the impact of SVR on liver fibrosis stage using non-invasive measures. Baseline predictors of liver fibrosis regression were determined. **Methods**: fibrosis stage was determined using: elastography (shear wave, Aixplorer SuperSonic Imagine, France) or FibroTest (BioPredictive, France) as well as the APRI score, and FIB-4; at baseline and at 6 months intervals after end of treatment. **Results**: A total of 150 patients were prospectively enrolled, of them, 125 (54% male, 59±11 years, BMI 28±4, F3-4 89%) are currently being reported. Median follow up period was 12 months (IQR 7-15). Of the 79 patients with F4 and 31(39%) with F3 at baseline; 31(39%) and 26(79%) demonstrated improvement in fibrosis stage (defined as fibrosis stage ≥1) respectively at the end of follow-up. The median (IQR) liver stiffness decreased from 11.5(9.7-17)Kpa at baseline to 10.5(7.3-14.2)Kpa (p>0.0001) at 6 month, and to 8.5(6.8-12.5)Kpa (p>0.003) at 12 month post treatment. The median (IQR) fibrosis stage (using FibroTest) decreased from baseline 0.77 (0.75-0.88) to 0.58 (0.49-0.77) at 12month P=0.001. Using univariate analysis, the baseline negative predictors of fibrosis regression in cirrhotics were: splenomegaly (p> 0.001), BMI>29 (p=0.037), DM (p=0.048), esophageal varices (0.007), bilirubin (p>0.0001), albumin (p=0.003), AST (p=0.005), ALT(p=0.019), PLT(p>0.0001) and APRI cut off >2.1 and FIB-4 score cut off >2.55 (p>0.0001). In multivariate analysis splenomegaly (OR 0.002, p=0.007), DM (OR 0.029, p=.039), BMI >29 (OR 0.016, p=0.014) and FIB-4 score>2.55 (OR 0.023, p=0.047) were baseline negative predictors of fibrosis regression. None of the cirrhotic patients developed hepatic decompensation. One patient (0.9%) developed hepatocellular carcinoma. **Conclusions**: Following successful DAAs treatment the majority of our HCV patients with advanced fibrosis stage demonstrated significant improvement in liver fibrosis stage assessed by non-invasive methods. Advanced fibrosis stage and the metabolic syndrome were negative predictors of fibrosis regression. Longer follow up period is required to determine the impact of DAAs treatment in HCV patients.

Abstract #623

Fibrosis monitoring after SVR

HCV

Transient Elastography Changes During Hepatitis C Treatment with Novel Agents

S Satyavada, R Zachariah, MB. Murphy, A B. Post

Past studies have demonstrated regression in fibrosis with interferon based treatments, however, currently studies are limited showing fibrosis scores before and after treatment with the newer oral Hepatitis C treatment modalities. **Methods:** This was a single center retrospective chart review at a major academic medical center that included patients prescribed one of the Direct-Acting Antiviral Drugs (DAAs) from January 2015 to November 2016. Pre and post (after SVR12) treatment fibroscan or FibroSURE (FibroTest) scores were recorded. **Primary outcomes** were: Median fibrosis scores pre and post SVR 12. Secondary outcomes included: median treatment time, median time to post treatment fibrosis score after SVR 12, distribution of pre and post SVR 12 fibrosis scores, and quality of change in fibrosis score post treatment. **Results:** Overall, 833 patients were prescribed a DAA; of those prescribed, 55 patients had completed HCV therapy, achieved SVR12, and had pre and post treatment fibroscan or FibroSURE (FibroTest) data available. Of these 55 patients, 20 patients had pre and post treatment fibroscan data, 30 patients had pretreatment FibroSURE (FibroTest)s and post treatment fibroscans, and 5 patients had pre and post-treatment FibroSURE (FibroTest) data. Median treatment time was 12 weeks and median time to post treatment F score after SVR 12 was 6 months. Outcomes are summarized in Table 1. **Conclusions:** This study suggests that treatment of chronic hepatitis c leads to early stability or slight improvement in fibrosis as measured by non-invasive means in the majority of patients who achieve SVR 12 after being treated with a DAA. Future studies should continue to monitor for improvements in fibrosis over time.

Abstract #1031

FibroTest to prioritize patients for DAA treatment

HCV

Fast-track HCV check-up enhances possibility of sustained virological response in HCV infected patients

T Antonini, M Tateo, P Attali, E De Martin, A Coilly, B Roche, R Sobesky, D Samuel, AM Roque- Afonso, J-C Duclos-Vallee

Background: New direct acting antiviral (DAA) against chronic hepatitis C virus (HCV) have drastically changed and shortened duration of treatments. However, the "HCV care course" (from diagnosis to sustained virological response (SVR)), represents an important challenge. **Aim:** To evaluate the impact of a new fast-track HCV check-up in terms of retention in care and SVR. In order to assess the efficacy we provide a comparison between the first 50 pts of the FT-HCV (Fast track HCV check-up) in 2016 to 50 pts followed in our "standard" out clinic practice (control group (CG)) in 2015. **Methods:** FT-HCV is a new assessment unit of our center. In the same half-day, pts benefits of a complete assessment of liver function: blood test with HCV-Ab and HCV viral load, genotype (G) determination, FibroTest. and transient elastography. Three hours after admission, we were able to confirm HCV and to discus the eligibility to an HCV treatment in accord to regulatory framework. **Results:** Groups were comparable for age and sex: 50 pts of each group were analyzed (FT-HCV: Male n= 34 (68%), mean age: 49±14 years, naive n=43 (86%); CG: Male n= 35 (66.6%), mean age: 53±13 years, naive n=44 (88%)). In FT-HCV and CG fibrosis (F) was: mild F0-F2 n=15 (30%), F2 n=12 (24%), F3 n=10 (20%), F4 n=13 (26%), and F0-F1 n=18 (36%), F2 n=12 (24%), F3 n=9 (18%), F4 n=10 (20%), unknown n=1 (2%) respectively. All cirrhotics pts have compensated cirrhosis (Child A/MELD 8-10) in the 2 groups. Six pts (12%) in the FT-HCV group were excluded because HCV viral load was negative. G distribution in the FT-HCV and in CG was: G1 n=25(50%), G3 n=8 (16%), G4 n=11 (22%), and G1 n=29 (58%), G2 n=5 (10%), G3 n=7 (14%), G4 n=7 (14%), G6 n=6 (4%) respectively. Thirty (69%) and 26 (52%) pts received DAA in FT-HCV and CG. Reasons for the absence of treatment in FT-HCV and CG were: non reimbursement framework n=11 (25%); comorbidities (n=3 (6%)) and non reimbursement framework n=11 (24%); comorbidities (n=4 (8%) and lost of follow-up in 8 pts (16%), respectively. Mean delay and numbers of out-clinic visits in FT-HCV and CG for treatment were 108 days (± 84) versus 260 days (± 85) p=0.009 and 2 (2-5) vs 4 (2-9) p=0.0003, respectively. To date in FT-HCV pts: SVR was achieved in 19 pts (63.3%), treatment is on-going in 5 pts (17.7%), waiting for SVR12 in 5 pts (17.7%) and 1 pt was not responder (3%). Complete results SVR 12 for all pts will be presented. In CG SVR was achieved in 23 pts (88%), 1 pt was non responder (3%) and 2 pts (6%) were lost of follow-up **Conclusion:** FT-HCV is a performing assessment of HCV infected patients and it allows increase in terms of retention in care, management and rates of SVR.

Abstract #1549

FibroTest to prioritize patients for DAA treatment

HCV

Efficacy and safety of sofosbuvir and daclatasvir for 8 weeks in treatment-naïve non-cirrhotic patients with chronic HCV Genotype 3 Infection

C Hezode, V Leroy, I Rosa, F Roudot-Thoraval, S Fourati, J-M Pawlotsky, V de Ledinghen, J-P Bronowicki

Background and Aims: HCV GT 3 is the second most common GT worldwide. For non-cirrhotic patients with HCV GT 3 infection, the EASL and AASLD/IDSA guidelines recommend treatment with the IFN- and RBV-free regimen of DCV + SOF or VEL/SOF for 12 weeks. The objective of this pilot study was to investigate the efficacy and safety of 8 weeks of DCV + SOF in treatment-na.ve patients with HCV GT 3 infection without cirrhosis. **Methods:** This ongoing pilot study is a multicenter, open label, single-arm trial that enrolled treatment-na.ve GT 3 patients without cirrhosis. Key exclusion criteria included the presence of cirrhosis, as determined by either a FibroScan score ≥12.5 kPa or a FibroTest score of ≥0.75, and baseline HCV RNA level >6,000,000 IU/mL. The regimen was DCV 60 mg plus SOF 400 mg once daily for 8 weeks. Efficacy was calculated as the percent of patients achieving SVR12 (HCV RNA <LLOD). Additional endpoints included the proportion of patients experiencing virologic breakthrough or relapse. Adverse events and clinical laboratory abnormalities were monitored to assess safety and tolerability. Analysis of baseline NS5A RASs at baseline and at the time of failure is ongoing. **Results:** 56 patients were included: mean age: 48±11 years, median FibroScan score: 7.3 kPa (range: 4.0-11.5), median HCV RNA level: 5.65 Log10IU/mL (range: 5.12-6.22). NS5A RAS testing at baseline was performed in 28 patients (ongoing in the remaining subjects): Two of them harbored NS5A RASs at baseline: A30V (n=1), S62L/Y93H (n=1). The SVR4 and SVR12 rates were 92% (44/48) and 92% (44/48), respectively. Four patients relapsed: one of them (FS=5.8 kPa) was poorly compliant; one (FS=8.4 kPa) had NS5A RASs at baseline (S62L/Y93H); one (FS=8.8 kPa) had no NS5A RAS at baseline, was compliant, but selected A30K/Y93H at the time of relapse; resistance testing is ongoing in the remaining patient (FS=9.2 kPa). SVR12, relapse and resistance data from the full series will be presented at the meeting. **Conclusions:** An 8-week regimen of DCV + SOF regimen appeared to be suboptimal in treatment-naive patients with chronic HCV GT3 infection without cirrhosis. Our results confirm that 12 weeks is the appropriate duration in this group of individuals.

Abstract #955

FibroTest for cirrhosis diagnosis in HBV trial

HBV

Correlations of baseline and early changes in bone and renal tubular biomarkers with BMD changes on TAF/ TDF treatment

P Lampertico, N Izumi, M Elkhashab, X Ma, V Suri, S Mo, JF. Flaherty, A Gaggar, M Subramanian, D Abdurakhmanov, K T Yoon, A Chowdhury, W-K Seto

Background: Results from two phase 3 studies comparing TAF with TDF have demonstrated improved bone safety with TAF treatment. The identification of patients at baseline and early in treatment who are at risk for developing significant bone disease can help in optimizing antiviral regimens. Here, we evaluate renal and bone biomarkers at baseline and after 24 weeks of TAF or TDF therapy to evaluate associations with BMD declines at Week 96. **Methods**: In two identically-designed Phase 3 studies of TAF, patients were randomized 2:1 to TAF 25 mg QD or TDF 300 mg QD, each with matching placebo. Renal Biomarkers (serum and urine phosphate (PO_4), serum and urine calcium (Ca), serum Ca:PO_4 ratio and markers of tubular dysfunction (RBP and B2M) and bone biomarkers (PTH, BsAP, OC, CTX and P1nP) were serially measured throughout the study and were used in the analysis; correlations were calculated using Spearman Correlation coefficients. **Results:** The 1298 patients in this analysis were 37% female, 9% with a FibroTest score >0.75, had a mean (SD) eGFR of 110 (28.2) mL/min, and a mean (SD) BMD hip (0.96 (0.146)) and spine (1.06 (0.172)). 1% and 7% had osteoporosis by hip and spine t-scores, respectively. At baseline, among serum bone biomarkers, serum OC had the strongest correlation with urine tubular markers (correlation coefficient -0.14 and -0.17, p<0.0001). Baseline bone and renal biomarkers overall are weakly correlated with Week 48 and 96 BMD declines, with the highest correlation seen with baseline sPO_4 (correlation coefficient -0.1; p=0.0015). When evaluating >3% declines in spine BMD at Week 96, the strongest baseline associations were with urine RBP (coefficient -0.12; p<0.0001). >3% declines in hip and spine BMD at Week 96 were significantly associated with week 24 on treatment changes in B2M (coefficient -0.095 and -0.10 p=0.0016 and 0.0008) as well as the bone biomarkers except PTH (all p<0.0001). By multivariate analyses, higher baseline RBP and sPO_4 levels were factors associated with greater declines in BMD at week 96, while at week 24, TDF treatment and increases from baseline in CTX and sCa were most significantly associated (table 1). **Conclusions**: Bone and renal (particularly the tubular) biomarkers appear to correlate with changes in BMD. These data suggest that biomarkers may be useful early surrogates for BMD change over time. The role of these markers as predictors of BMD change will require further validation.

Abstract #2214

NASH Correlations

NASH

Predictors of Fibrosis Progression and Regression by Histology and Morphometrically Quantified Collagen in Patients with Nonalcoholic Steatohepatitis (NASH) and Advanced Fibrosis

ZM Younossi, M Stepanova, AJ Sanyal, SA Harrison, V Ratziu, BJ McColgan, RP Myers, M Subramanian, JG McHutchison, NH Afdhal, MF Abdelmalek, J Bosch, ZD Goodman.

Background: Hepatic fibrosis is the best predictor of mortality in NASH. Factors associated with progression or regression of fibrosis in NASH unknown. **Our aim** was to determine factors associated with progression or regression of fibrosis in patients with NASH and advanced fibrosis who underwent multiple liver biopsies in clinical trial setting. **Methods**: Adults with advanced fibrosis (NASH CRN stages 3-4) were enrolled in two phase 2b controlled trials of simtuzumab. Baseline (BL) and week 96 biopsies were stained for collagen and alpha smooth muscle actin (aSMA) and quantified using computer-assisted morphometry. BL clinico-laboratory data, serum fibrosis biomarkers [hyaluronic acid (HA), N-terminal procollagen III propeptide (PIIINP), tissue inhibitor of metalloproteinase-1 (TIMP-1)], and predictive fibrosis scores [Enhanced Liver Fibrosis (ELF), FibroTest, APRI, FIB-4, NAFLD Fibrosis Score (NFS)] were used. Fibrosis progression (only in stage 3) was defined histologically by 1-stage increase or its best correlate morphometrically (>20% increase in % of collagen deposition) from BL. Fibrosis regression (in both stage 3 or 4) was defined histologically (≥1-stage decrease) or its best correlate morphometrically (>30% decrease of % collagen). Univariate and multivariate multivariate analyses (MVA, a logistic regression model with stepwise selection) were performed to determine independent predictors of progression or regression of fibrosis. **Results**: 466 subjects with advanced fibrosis and complete data were included (age 54 yrs, 63% female, 67% diabetic, 53% cirrhosis [n=248]). In follow-up, histologic progression was seen in 42 (19%) patients with BL stage 3 fibrosis [morphometric – in 55 (25%)]; histologic regression – in 63 patients (13%) of all subjects [morphometric – in 179 (40%)]. In MVA, risk of histologic fibrosis progression was independently associated with higher BL ELF score [odds ratio (OR) = 2.79 (95% CI=1.85-4.21) per 1 point], lower alkaline phosphatase (ALP) (OR=0.986 (0.973-0.999) per U/L), and higher aSMA expression [OR = 1.15 (1.05-1.26) per 1 percent); all $p<0.03$]. Fibrosis progression by morphometry was predicted only by higher BL HA (OR =1.006 (1.003-1.009) per 1 ng/mL, $p<0.0001$). In contrast, histologic fibrosis regression was predicted by lower BL levels of aSMA expression, lower BL HbA1c, FIB-4 and ELF but higher BL ALP ($p<0.05$). Finally, morphometric fibrosis regression was independently associated with lower BL TIMP-1 & higher platelet count ($p<0.01$). **Conclusions**: These data suggest that a combination of baseline clinical factors and serum fibrosis markers are associated with fibrosis changes in NASH. Further validation is needed. serum fibrosis markers are associated with fibrosis changes in NASH. Further validation is needed.

Abstract #2217

NASH Correlations

NASH

Hepatic de novo lipogenesis is elevated in patients with NASH independent of disease severity

E Lawitz, K Li, J Tarrant, M Vima, R Xu, Q Song, RE Aguilar Schall, BJ McColgan, CS Djedjos, AS Ray, RP Myers, MK Hellerstein, R Loomba

Background: Elevated de novo lipogenesis (DNL) contributes to the pathogenesis of NASH via synthesis of lipotoxic mediators, inhibition of fatty acid oxidation, and the hepatic deposition of lipid. **Our objective** was to quantify hepatic DNL in subjects with NASH and determine associations with clinical characteristics including measures of disease severity. **Methods**: We evaluated 10 healthy controls (18-45 years, BMI 19-28 kg/m2, normal liver biochemistry) and 30 subjects with NASH diagnosed noninvasively by a hepatic proton density fat fraction (PDFF) >10% by MRI and liver stiffness >2.88 kPa by MR elastography (MRE). Heavy water (2H2O, 35 mL) was administered three times daily for one-week with blood drawn at day 14 following initiation of heavy water. Deuterium incorporation into palmitate in whole plasma was measured in fasting samples by gas chromatography mass spectrometry with kinetic modeling to calculate hepatic DNL. In NASH subjects, associations between DNL and clinical characteristics including demographics, diabetes, glycemic indices, fasting serum lipids, liver biochemistry, serum fibrosis markers, MRI-PDFF, and MRE-stiffness were evaluated. **Results**: The median age of the NASH subjects was 55 years, 77% were female, 70% had diabetes, and median body weight was 94 kg. Median MRI-PDFF was 15.6% (IQR 12.9- 20.1%) and MRE-stiffness was 3.38 kPa (3.12-3.86 kPa). Compared with healthy controls, peak fasting hepatic DNL after 14 days of label exposure was significantly greater in subjects with NASH (median: 18% [IQR 11-34%] vs. 37% [30-45%]; p=0.003). In NASH subjects, hepatic DNL did not differ according to age, sex, or diabetes, and no significant correlations were observed with glycemic indices (fasting glucose, insulin, HbA1c, or HOMA-IR), body weight, liver biochemistry (AST, ALT, GGT), or serum fibrosis markers (ELF, FibroTest). Hepatic DNL was positively correlated with fasting triglycerides (Spearman ϱ=0.51; p=0.004) and VLDL-C (ϱ=0.51; p=0.004), but not LDL-C or HDL-C. DNL was not correlated with MRI-PDFF (ϱ=-0.27; p=0.15) or MRE-stiffness (ϱ=-0.10; p=0.60). Median hepatic DNL was similar in subjects with MRE-stiffness < vs. ≥3.64 kPa (~ F0-2 vs. F3-4: 38% vs. 36%; p=0.79). **Conclusions**: In patients with NASH, hepatic DNL is consistently elevated across the range of disease severity. These data support targeting DNL (e.g. with acetyl-CoA carboxylase inhibition) for the treatment of NASH across the spectrum of disease.