AASLD 2014

FibroTest/FibroSure Scientific Publications
Oral Communications and Posters for AASLD 2014

Poster Session 2

Clinical Steatohepatitis

#836

SUNDAY NOVEMBER 9

Performance of FibroMax (SteatoTest, ActiTest, FibroTest) in patients with NAFLD for predicting liver lesions (Steatosis, Activity and Fibrosis) assessed by SAF scoring system and FLIP algorithm

Mona Munteanu, Fabio Nascimbeni, Pierre Bedossa et al.

Background. FibroMax is a panel of blood tests assessing the severity of fibrosis (FibroTest), steatosis (SteatoTest), and necro-inflammatory activity (ActiTest and NashTest). In contrast with viral hepatitis (specific scoring system METAVIR, extensive validations), blood tests have been less validated in NAFLD patients (pts). Recently (Hepatology 2014), SAF score (S=Steatosis; A=Activity; F=Fibrosis) and FLIP algorithm have permitted to categorize liver lesions in NAFLD and to identify histologically severe forms (HSF, as A≥3 and/or F≥3). The aim was to validate FibroMax using SAF/FLIP in NAFLD pts.

Methods. Pts from 2 NAFLD cohorts (consecutive metabolic risk factors' pts, tertiary center, cohort 1) and multicenter NASH therapeutic trial (cohort 2), were included if interpretable biopsies have been centrally and blindly reassessed with SAF/ FLIP algorithm, and contemporaneous FibroMax prospectively assessed according to analytical recommendations, applicability algorithms and previously validated cutoffs. For categorical scores area under the AUC (AUROCs) were assessed with Obuchowski measures (weighted AUROCs between all combinations of SAF scores preventing spectrum effect), were performed per protocol (PP) and in intention to diagnose (ITD).

Results. 207 pts were included; 60% male, median age 54yr, BMI 29, biopsy length 25mm; according to SAF/FLIP: 16(8%) were classified as not-NAFLD (steatosis<5%), 64 (31%) as Ste-atosis without NASH and 127 (61%) as NASH. Performances of blood tests were highly significant (Table; all P<0.001) for predicting SAF scores and FLIP categories. Sensitivity analyses performed in ITD, according to cohorts, gender and biopsy specimens length gave similar results.

Conclusion: Non invasive blood tests such as SteatoTest, ActiTest and Fibrotest were accurate for predicting steatosis, activity and fibrosis (histo-logical SAF scores) in patients with NAFLD, with and without NASH.

FibroMax blood tests performance for the diagnosis of SAF/FLIP algorithm

Blood test	FibroTest	SteatoTest	ActiTest	ActiTest
Liver lesion (SAF score range)	Fibrosis (0-4)	Steatosis (0-4)	Activity (0-4)	NASH (yes-no)
Measure	Obuchowski	Obuchowski	Obuchowski	AUROC
Result mean (SE)	0.869 (0.014)	0.803 (0.018)	0.846 (0.016)	0.699 (0.037)
Significance	P<0.001	P<0.001	P<0.001	P<0.001

FibroTest/FibroSure Scientific Publications
Oral Communications and Posters for AASLD 2014

Poster Session 2

Clinical Steatohepatitis

#843

SUNDAY NOVEMBER 9

Endoscopic Duodenal–Jejunal Bypass Liner (Endobar-rier) Improves Hepatic Parameters of Nonalcoholic Fatty Liver Disease in Obese Uncontrolled type 2 Diabetes Mellitus Patients

Oranit Cohen-Ezra, Gabriella Segal-Lieberman, Alon Lang et al.

Background. Nonalcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease in Western countries, may progress to cirrhosis, liver failure, and complicated hepatocellular carcinoma. Recently, a nonsurgical bariatric technique, the Endobarrier (GI Dynamics), an endoscopically-delivered device that mimics gastric bypass surgery by shielding the duodenum and upper jejunum from contact with chyme was reported to lead to significant weight loss and to rapid improvement of type 2 diabetes, both conditions are important risk factors for NAFLD.

Aims. We therefore investigated the effect of Endobarrier treatment on hepatic parameters in obese uncontrolled type 2 diabetes mellitus patients with NAFLD.

Methods.The Endobarrier device was implanted for 12 months in the duodenum via an endo-scopic procedure in 44 uncontrolled diabetic, obese, NAFLD subjects (age 52.3±9.3y, 52.2% male, BMI 37.5±4.6 m2/kg). BMI, waist circumference, serum liver enzyme levels, glucose, HBA1c and lipid profile were performed as well as shear wave elastography (SWE) (Aixplorer SuperSonic Imagine, France) and Fibromax (FibroTest, ActiTest, SteatoTest, and NashTest) (BioPredictive, France) for the noninvasive evaluation of hepatic injury before, 3 and 6 months during the implantation of the Endobarrier device and when removing the device (12 months).

Results. At 3 and 6 months after implantation of the Endo-barrier (interim results, n=29), the BMI, waist circumference, serum liver enzyme levels, glucose, HBA1c and lipid profile decreased significantly (from baseline and from 3 to 6 months). The fibrosis stage (evaluated by SWE) and the: SteatoTest (fat liver content), and NashTest (steatohepatitis score) (evaluated by Fibromax) also improved significantly from baseline and from 3 to 6 months. In 9 subjects (20.4%) the Endobarrier was endoscopically explanted early.

Conclusion: Endobarrier, a minimally invasive bariatric technique, achieved significant improvement in hepatic injury, fat liver content, steatohepatitis score and fibrosis stage in advanced uncontrolled obese, diabetic, NAFLD patients. This device may be suitable for the treatment of morbid obesity and its related comorbidities including NAFLD.

ORAL Parallel 8

Novel Approaches in Diagnosis and Treatment in NAFLD and NASH

#57

SUNDAY
NOVEMBER 9
3.30 PM

Early phase 1 clinical trial results of GR-MD-02, a galectin-3 inhibitor, in patients having non-alcoholic steatohepatitis (NASH) with advanced fibrosis

Stephen A. Harrison, Naga P. Chalasani, Eric Lawitz et al.

Introduction: NASH with fibrosis is a significant cause of liver disease in which effective therapies are limited. Galectin-3 is a critical protein in the pathogenesis of liver fibrogenesis and NASH. GR-MD-02, a galectin-3 inhibitor, has beneficial therapeutic effects in rodent models of NASH and toxin-induced cirrhosis.

Methods: The phase 1 trial was designed as a multi-center, partially blinded (patients, PI and staff), maximum tolerated multiple dose escalation study in patients with biopsy proven NASH having stage 3 fibrosis. In the first cohort, 8 patients were randomized to receive 4 doses of either placebo (2 patients) or 2 mg/kg lean body weight (lbw) of GR-MD-02 (6 patients) by intravenous infusion on days 0, 28, 35 and 42. Drug levels were measured following the first and fourth doses. Serum biomarkers associated with fibrosis (including FibroTest® and the Enhanced Liver Fibrosis (ELF) score), with inflammation (including IL-6, TNFα and IL8), serum levels of aminotransferases, and keratin 18 (K-18, also known as CK-18) were assessed at day -1 and day 56.

Results: GR-MD 02 was safe and well tolerated following 4 doses of 2 mg/kg lbw with no treatment-associated adverse events. The pharmacokinetics were consistent between individuals and after single and multiple doses with no drug accumulation. FibroTest® scores were significantly reduced in GR-MD-02 treated patients (-27% ±5.8 (SEM)) compared to placebo patients (3.5% ±20.5, p=0.04, α<0.1). Although there was a tendency towards reduction in ELF scores in treated patients (-3.8% ±1.2) compared to placebo (-2% ±2), the difference did not reach significance (p=0.2, α<0.1). Patients treated with GR-MD-02 also had significant reductions in serum biomarkers associated with inflammation when compared to patients treated with placebo, including IL-6 (-16% ±4.7 vs. 6.5% ±4.5, p=0.02, α<0.1), TNFα (-16% ±6.9 vs. 20% ±30, p=0.06, α<0.1), and IL-8 (-25.5% ±3.6 vs. -3.5% ±12.5, p=0.02, α<0.1). Additionally, patients with greater evidence of liver cell injury, as indicated by elevated serum aminotransferase levels, had a marked decrease in serum K-18. Galectin-3 blood levels, which do not correlate with tissue levels in animal models of NASH, were not changed with treatment.

Conclusions: This first human study of the galectin-3 inhibitor GR-MD-02 achieved its primary safety endpoint at a dose of 2 mg/kg. Additionally, this initial dose showed improvement in serum biomarkers of fibrosis and inflammation suggesting a potential beneficial disease effect. The clinical trial is ongoing using a dose of 4 mg/kg of GR-MD-02, which will be followed by an 8 mg/kg dose cohort.

ALCOHOL
Poster Session 3

Alcohol: Clinical and Basic Mechanisms

#1225

MONDAY
NOVEMBER 10

Repeated validation of AshTest as a non-invasive alternative to liver biopsy in patients with suspicion of severe acute alcoholic hepatitis (AH)

Marika Rudler, Sarah Mouri, Frederic Charlotte et al.

Background: According to guidelines, diagnosis of severe AH requires liver biopsy among patients (pts) with recent onset of jaundice and a Maddrey discriminant function (DF) >32. AshTest, a combination of the 6 components of FibroTest-ActiTest plus aspartate aminotransferase have been validated for the diagnosis of AH in a large population of heavy drinkers (J Hepatol 2006).

The aim was to repeat the AshTest validation in pts with alcoholic cirrhosis and suspicion of severe AH in order to reduce the need for biopsy.

Methods: AshTest was prospec-tively assessed in pts admitted in ICU for suspicion of AH who fulfilled the following criteria: 1) jaundice >3 months, 2) DF >32 at admission, 3) bilirubin>50 Limol/l, 4) active drinking. Exclusion criteria was advanced hepatocellular carcinoma. The gold standard was biopsy systematically performed using tran-sjugular route, assessed by the standard criteria (polymorpho-nuclear PNN with hepatocellular necrosis and its histological severity jn 4 classes: none, mild, moderate and severe) by the same experienced pathologist blind to simultaneous NashTest results. NashTest was performed on fresh serum according to analytical recommendation ad analyzed using the same cutoffs than in the previous studies.

Results: AshTest was not applicable in 2 pts. A total of 108 patients were included: male gender 76%; median age was 56yr, Child-Pugh score 11, MELD score 23, DF 54, AshTest 0.87, FibroTest 0.97 (all F4), Biopsy length 15mm, and number of fragments 10. Prevalence of moderate/severe histological severity was 89%; intermediate/severe scores' prevalence were 54%, 29% and 30% for ballooning, PNN and Mallory bodies respectively. All pts with severe AH received prednisolone.Performances of AshTest (Table) assessed by Obuchowski measures for semi-quantitative scoring system and AUROCs for binary outcome, were highly significant for the main endpoint (HA), or ballooning, PNN and Mallory bodies, similarly to previous results obtained in heavy drinkers. At a 0.5 cut-off, the positive predictive value was 0.95. Only one case was a clear false positive of AshTest due to cardiac insufficiency.Other discordances could be also due to false negative of small biopsies.

Conclusion: This study confirmed the performance of AshTest as a non-invasive alternative of transjugular liver biopsy in cirrhotic patients with suspected severe acute alcoholic hepatitis who need specific treatment.

FibroTest/FibroSure Scientific Publications
Oral Communications and Posters for AASLD 2014

Poster Session I

Immunosuppression
Saturday

#534

SATURDAY
NOVEMBER 8

Abusive drinking after liver transplantation for pure alcoholic cirrhosis is associated with significant allograft fibrosis

Marika Rudler, Géraldine Rousseau, Pascal Lebray et al.

Background. Progression of fibrosis after liver transplantation(LT) is associated with a worse outcome. One study suggested that abusive drinking after LT for pure alcoholic cirrhosis was associated with liver fibrosis progression. Aims (1) to evaluate alcohol consumption in France after LT for alcoholic cirrhosis using carbohydrate deficient transferrin (CDT); (2) To assess fibrosis progression using 2 non-invasive methods.

Methods Liver fibrosis progression was assessed using FibroTest (FT, Biopredictive, France) and FibroScan (FS, Echosens, France) in all patients who underwent LT for pure alcoholic cirrhosis in our center, on the same day, once a year. Discordances between the 2 methods were resolved by consensus, after repeating the tests and analysing the files of each patients (clinical examination, biology, ultrasound exam). Excessive drinking was defined by a CDT>1.8%. Parameters of metabolic syndrome were assessed each year.

Results Overall, 93 patients were transplanted in La Pitié-Salpêtrière (Paris, France) for pure alcoholic cirrhosis, all other causes of hepatopathy being ruled out, between February 2000 and June 2012. Among them, 9 died within the first year after LT, and 9 were not evalu ated (lost of follow-up or residing in a foreign country). 75 patients were prospectively analyzed (male gender: 77,3%; age at LT: 55,4±7,2 years; indication for LT: hepatocellular carcinoma 26,7%, end-stage liver disease 72%, or portal hypertension 1,3%). Mean follow-up was 64 months (16-158). Follow-up was at least of 1 year in all patients, 2 years in 96% of patients, 3 years in 86.7% and 4 years in 68% of patients. FibroTest was applicable in 74/75 patients (98.6%) and FibroScan in 68/75 patients (90.7%). Three patients (4%) declared an excessive alcohol consumption, whereas 27 (36%) had a CDT>1.8%. Overall, 36% of patients developed significant fibrosis (F≥2). Independent factors associated with the development of significant fibrosis were weight at evaluation (p=0.003), cold ischemia (p=0.05), and alcohol abuse (p=0.04), but not the development of metabolic syndrome after LT.

Conclusion Alcohol consumption is underestimated after LT for pure alcoholic cirrhosis and should be evaluated with objective biomarkers such as CDT. Abusive drinking after LT is associated with significant progression of fibrosis that should be regularly assessed with noninvasive methods.

HBV FOLLOW-UP

Poster Session 4

Hepatitis B Therapy
Tuesday

#1922

TUESDAY
NOVEMBER 11

2-years impact of entecavir (ETV) on liver fibrosis and activity as assessed by FibroTest – ActiTest and Liver Stiffness Measurement (LSM) in chronic hepatitis B (CHB) patients

Fabien Zoulim, Xavier Causse, Vincent Leroy, et al.

Background. Fibrosis-regression(FR) rate in treated CHB-patients patients was similary estimated using Fibrotest and LSM (Fibroscan), although with possible overestimation of FR by LSM related to necroinflammatory activity(NIA).(AntivirTher2009,2010)

Aims. To prospectively evaluate : 1)The histological impact of strong inhibitor of HBV-replication, entecavir-motherapy [0.5mg/day], using Fibrotest-Actitest and LSM.2) The impact of presumed steatosis(Steatotest) on the treatment response.

Methods. NUC-naive CHB preincluded [19-centers,France] followed-up (FU) from baseline to M6,M12 and M24-months. Viral-response(VR) defined as undetectable-HBVDNA.

Results. N=177 pre-included, 15-retracted, 3-died, 5 non-applicable Fibrotest (4 flare-up ALT>600IU/L), 24 lost-of-follow-up (FU); N=137 with M6-FU included [age 45(20-83)yrs; 71%males; 84% anti-HBe(+); 43%caucasian/29%asian/28%african]. Applicable-LSM vs Fibrotest 95%vs97.2%(p<0.0001). Fibrotest presumed advanced fibrosis(AF,F2F3F4-METAVIR) in 36%(60/167) and cirrhosis 12%(N=20/167); presumed NIA (Actitest) in 74%(123/166) and baseline steatosis>1% (Steatotest) 37%(57/156). N=43 had liver biospy [size 24(5-40)] AF 56%(24/43). VR prevalences were 67% M6(N=120), 83% M12(N=105) and 86%M24(N=50). Presumed NIA [Actitest] regressed from M0 0.38(0.02) to M6 0.21(0.01), M12 0.19(0.01) and M24 0.14(0.02), all p<0.0001vsM0. 76% patients with baseline-NIA regressed at M6. Presumed AF [Fibrotest] regressed from M0 0.69(0.02) vs M6 0.59(0.03) vs M12 0.57(0.03), M24 0.60(0.04), all p<0.01vsM0. M12-FR patients had lower prevalece of baseline steatosis>5% (Steatotest) than those without: 40%vs8%,p=0.003. FR using LSM from baseline to M6 (NS) and to M12 [N=23; 8.6(4.2) vs6.2(0.4)kPa,P=0.001)]. Regardless VR, M12 AF-prevalences decreased [39%vs30%,p=NS]; M12-VR had lower remaining NIA versus non-VR (17%vs56%,p=0.01).

Conclusion. Twelve months entecavir, reduced significantly AF and NIA presumed by Fibrotest-Actitest and LSM, regardless of the viral response. Patients without M12-FR had more baseline steatosis presumed by Steatotest.

FibroTest/FibroSure Scientific Publications
Oral Communications and Posters for AASLD 2014

HCV DAA TRIALS USING FIBROTEST FOR CIRRHOSIS DIAGNOSIS

Poster Session 4

Hepatitis C: New Agents (Not Approved)

#1937

TUESDAY NOVEMBER 11

All-oral Dual Combination of Daclatasvir plus Asunaprevir Compared with Telaprevir plus Peginterferon Alfa/Ribavirin in Treatment-naive Japanese Patients Chronically Infected with HCV Genotype 1b: Results from a Phase 3 Study

Kazuaki Chayama, Fumitaka Suzuki, Yoshiyuki Suzuki et al.

Background: Daclatasvir plus asunaprevir dual oral therapy (DCV+ASV) has demonstrated high SVR rates in Japanese HCV genotype (GT) 1b patients. In this Japanese phase 3 study of GT1b patients (AI447-031), the safety and efficacy of DCV +ASV were compared to telaprevir plus peginterferon alfa-2b and ribavirin (TVR+P/R) in treatment-naive patients. A single arm assessed DCV+ASV in prior peginterferon/ ribavirin relapsers. This study represents the first head-to-head comparison of an all-oral regimen vs TVR+P/R.

Methods: Treatment-naive patients were randomly assigned to receive either DCV 60mg QD plus ASV 100mg BID (N=119) for 24 weeks or TVR 750mg TID plus P/R for 12 weeks then P/R for 12 weeks (N=111). Relapsers (N=22) received 24 weeks therapy with DCV 60mg QD plus ASV 100mg BID. The primary endpoint was the proportion of naive patients with sustained virologic response at posttreatment Week 12 (SVR12).

Results: Baseline characteristics were comparable in the DCV+ASV and TVR+P/R arms (median age: 57 vs 56 yrs; female: 60% vs 51%; IL28BCC: 66% vs 67%; mean baseline HCV RNA: 6.84 vs 6.76 log10IU/mL). The median age of relapse patients was 65 yrs, 68% were female, 73% were IL28BCC and mean baseline HCV RNA was 7.01 log10IU/ mL. SVR12 rates were higher among treatment-naive patients receiving DCV+ASV vs TVR+P/R (Table; treatment difference 26% [95% CI: 16,36]). No differences in SVR12 for DCV+ASV were observed based on age, IL28B, baseline HCV RNA, or fibrotest score in naive patients. High SVR12 rates were observed in relapsers treated with DCV +ASV (21/22; 95%). Serious adverse events occurred in 4% and 5% of naive patients receiving DCV+ASV or TVR+P/R. Discontinuations due to AEs were reported in 5% and 20%, respectively; no deaths occurred. Rates of anemia (<10 g/dL) and rash-related events with DCV+ASV were superior to TVR+P/R: 0% vs 48% and 0% vs 14%, respectively. Grade 3/4 ALT lab abnormalities were observed more frequently with DCV+ASV (13% vs 3% with TVR+P/R). Five DCV+ASV patients discontinued due to ALT elevations; all achieved SVR12. The DCV+ASV safety profile in relapsers was comparable to naive patients.

Conclusion: Dual therapy with DCV+ASV achieved higher rates of SVR12 (89%) compared to TVR+P/R (62%) in treatment-naive Japanese GT1b patients. DCV+ASV therapy was well tolerated and associated with lower rates of anemia and rash-related events.

FibroTest/FibroSure Scientific Publications
Oral Communications and Posters for AASLD 2014

Poster Session 4

Hepatitis C: New Agents (Not Approved)

#1943

TUESDAY NOVEMBER 11

Daclatasvir in combination with asunaprevir and BMS-791325 for prior null responders with chronic HCV genotype 1 infection

Gregory T. Everson, Karen D. Sims, Paul J. Thuluvath et al.

Introduction: The all-oral, ribavirin-free combination of daclatasvir (DCV; NS5A inhibitor), asunaprevir (ASV; NS3 inhibitor), and BMS-791325 ('325; non-nucleoside NS5B inhibitor) is being evaluated in a phase 2 randomized clinical trial (AI443-014). Previously, sustained virologic response (SVR12) was achieved by 92% of treatment-naïve patients with chronic HCV genotype (GT)1 infection and 100% with GT4. In a study expansion (AI443-014), this regimen was evaluated in patients with GT1 infection and prior null response to peginterferon/ribavirin.

Methods: HCV GT1-infected null responders with GT1 infection were randomly assigned (1:1:1:1) to receive a twice-daily regimen of DCV 30mg, ASV 200mg, and '325 75mg or 150mg for 12 or 24 weeks. Randomization was stratified by GT1 subtype (up to 40% GT1b) and presence of biopsy-confirmed cirrhosis (up to 10% per group). The primary endpoint was HCV RNA <LLOQ (25 IU/mL) at 12 weeks posttreatment (SVR12).

Results: Across the 4 treatment groups, patients were 65% male, 67% white, 72% HCV GT1a, 59% Metavir F3/F4 (derived from baseline FibroTest score), 98% IL28B non-CC. SVR12 was achieved by 91% of patients overall, with similar results after 12 or 24 weeks of treatment (Table). All 4 biopsy-confirmed cirrhotic patients (1 per group) and all patients with GT1b infection (n=13) achieved SVR12. There were 3 on-treatment virologic breakthroughs (all by treatment Week 8) and 1 posttreatment relapse that occurred by follow-up Week 4; the resistance profile of these patients will be provided for presentation. There were 3 serious adverse events (AEs), all considered unrelated to DCV 3DAA treatment by the investigator, no AE-related discontinuations, and 3 treatment-emergent grade 3/4 lab abnormalities. None of the lab abnormalities required treatment interruption. The most frequent AEs were headache (33%), fatigue (26%), and pruritus (15%).

Conclusions: SVR12 was achieved by 91% of prior null responders with HCV GT1 infection after 12 or 24 weeks of all-oral treatment with DCV + ASV + BMS-791325. These results extend the potent antiviral activity and favorable tolerability and safety profile observed previously in treatment-naive patients.

FibroTest/FibroSure Scientific Publications
Oral Communications and Posters for AASLD 2014

Poster Session 4

Hepatitis C: New Agents (Not Approved)

#1955

TUESDAY NOVEMBER 11

Safety and efficacy outcomes of all-oral daclatasvir-containing regimens in patients with or without cirrhosis in phase 2 and 3 studies

Donald M. Jensen, Ira M. Jacobson, Hiromitsu Kumada et al.

Background: All-oral regimens of direct-acting antivirals may offer improved safety and efficacy for treatment of chronic HCV infection in patients with advanced fibrosis or cirrhosis. We compared outcomes by disease stage across studies of daclatasvir (DCV)-based oral regimens.

Methods: Safety outcomes from 2 phase 2 (AI447011, AI447017) and 2 phase 3 (AI447026, AI447028 [HALLMARK-DUAL]) studies of DCV + asunaprevir (ASV) in patients with genotype (GT)1b infection were pooled and analyzed by pre-treatment cirrhosis status. Efficacy (SVR12) was assessed by individual study. Similarly, safety and efficacy data from a phase 2 study (AI444040) of DCV + sofosbuvir (SOF) ± ribavirin (RBV) in patients with GT 1, 2, or 3 were assessed according to the presence or absence of advanced fibrosis, derived from FibroTest score: F3/F4–F4 (≥0.73) vs F0–F3 (<0.73).

Results: Frequencies of serious adverse events (SAEs), AEs leading to discontinuation, and treatment-emergent grade 3/4 lab abnormalities were similar in compensated cirrhotic and non-cirrhotic patients receiving DCV/ASV (Table). There were 10 SAEs and 2 AE-related discontinuations in the 040 study, none in the 32 patients with advanced fibrosis. In DCV/ASV phase 2 studies in non-cirrhotic patients (N=51), SVR12 was achieved by 73-78% of patients. In DCV/ASV phase 3 studies, SVR12 was achieved by 84-91% of cirrhotic patients (N=228) and by 84-85% of non-cirrhotic patients (N=637). In the 040 study of DCV/SOF ±RBV, SVR on or after posttreatment Week 12 was achieved by 100% of patients with advanced fibrosis (F3/F4–F4; N=32) and by 98% of patients with F0-F3 (N=179).

Conclusions: Safety and efficacy outcomes of all-oral combinations with daclatasvir are similar in patients with or without advanced fibrosis or cirrhosis, supporting the further development of these regimens in patients with advanced liver disease

FibroTest/FibroSure Scientific Publications
Oral Communications and Posters for AASLD 2014

Poster Session 4

Hepatitis C: New Agents (Not Approved)

#1958

TUESDAY NOVEMBER 11

No Differences in the Efficacy of Fixed-Dose Combination Ledipasvir/Sofosbuvir in Patients According to Fibrosis Stage Determined by Liver Biopsy or Laboratory Biomarker in Phase 3 Clinical Trials

Stuart C. Gordon, Michael W. Fried, Paul Y. Kwo, et al.

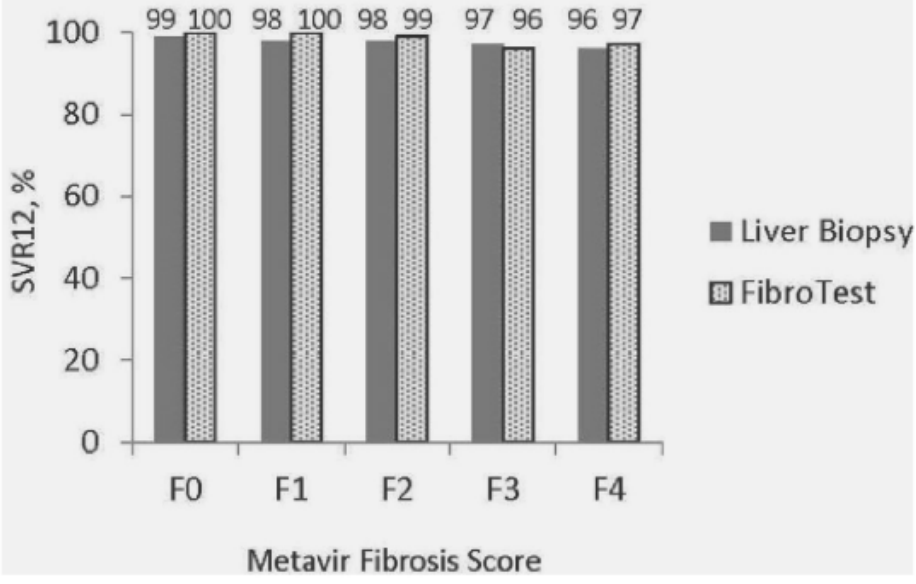
Background: Enrollment of a significant proportion of patients with fibrotic liver disease in the ledipasvir/sofosbuvir (LDV/SOF) Phase 3 program allowed for post-hoc analyses of the impact of fibrosis stage determined by various methods on treatment response.

Methods: Patients with liver biopsy and an interpretable laboratory biomarker (**FibroTest/FibroSure**) results were pooled across three LDV/SOF Phase 3 clinical trials (ION-1, ION-2, and ION-3). **FibroTest** results were then mapped to Metavir Fibrosis Score in the following manner: 0-0.21 (F0); >0.21-0.31 (F1); >0.31-0.58 (F2); >0.58-0.72 (F3); >0.72-1.00 (F4). Differences in SVR12 rates according to fibrosis stage as determined by liver biopsy and laboratory biomarker are reported.

Results: Of 1952 patients treated with a LDV/SOF-containing regimen, 986 (51%) had documentation of fibrosis stage by both liver biopsy (9% F0; 31% F1; 30% F2; 20% F3; 10% F4) and laboratory biomarker (8% F0; 6% F1; 27% F2; 23% F3; 36% F4). No difference in SVR12 was observed between patients with fibrosis stage as determined by liver biopsy (98% F0-F2; 97% F3; 96% F4) and those with fibrosis determined by laboratory biomarker (99% F0-F2; 96% F3; 97% F4) (Figure 1).

Conclusion: Ledipasvir/sofosbuvir-based regimens are effective in genotype 1 infected patients irrespective of the degree of fibrosis or the method of fibrosis determination.

Figure 1. SVR12 Rates According to Metavir Fibrosis Score Determined by Liver Biopsy and **FibroTest**



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Poster Session 4

Hepatitis C: New Agents (Not Approved)

#1962

TUESDAY NOVEMBER 11

TURQUOISE-II: Trends in Liver Fibrosis Testing, Hepatic Synthetic Function, and Platelet Counts at Baseline and 12 Weeks After Treatment With ABT-450/r/Ombitasvir and Dasabuvir With Ribavirin in HCV Genotype 1-Infected Patients with Cirrhosis

Mitchell L. Shiffman, Kris V. Kowdley, Stefan Zeuzem et al.

Purpose: Patients with cirrhosis are at risk for declines in hepatic synthetic function over time. Antiviral therapy may lead to fibrosis regression and hepatic synthetic function improvement if a sustained virologic response (SVR) is attained. ABT-450 is an HCV NS3/4A protease inhibitor (dosed with ritonavir, ABT-450/r) identified by AbbVie and Enanta. Ombitasvir (ABT-333) is an NS5A inhibitor; dasabuvir (ABT-267) is an NS5B RNA polymerase inhibitor. The phase 3 TURQUOISE-II trial examined efficacy and safety of all-oral regimens of co-formulated ABT-450/r/ombitasvir+dasabuvir with ribavirin (3D+RBV) in treatment-naïve and treatment-experienced patients with HCV genotype 1 infection and compensated (Child-Pugh A) cirrhosis. We report trends in surrogates for hepatic synthetic function and fibrosis scoring over time.

Methods: In this open-label trial, patients were randomized to receive 3D+RBV for 12 or 24 weeks. Changes in FibroTest score, laboratory surrogates for hepatic synthetic function, and alpha fetoprotein (AFP) between baseline and post-treatment week (PTW) 12 are presented.

Results: 380 patients were randomized and dosed. SVR12 rates in the 12-week and 24-week groups were 91.8% and 95.9%, respectively. Mean FibroTest score, international normalized ratio (INR), albumin level, platelet count, and AFP level each improved between baseline and post-treatment week 12 (Table). The improvement in each parameter was numerically greater for patients in the 24-week treatment group than those in the 12-week group.

Conclusions: In the phase 3 TURQUOISE-II trial, treatment with the 3D+RBV regimen for 12 or 24 weeks resulted in an improvement in hepatic synthetic function, FibroTest score, and AFP levels within 12 weeks after completion of antiviral therapy in patients with HCV genotype 1 infection and cirrhosis. Patients receiving 24 weeks of treatment had numerically greater improvements than patients receiving 12 weeks of treatment. This may reflect a longer duration since initial HCV RNA suppression in patients in the 24-week treatment arm. Further follow-up of patients with cirrhosis who achieve SVR will be important for assessing the magnitude and durability of these changes in surrogates of hepatic function and fibrosis

BL=baseline, PTW12=post-treatment week 12

	3D+RBV for 12 weeks				3D+RBV for 24 weeks			
	N	BL Mean	PTW12 Visit Mean	Mean Change from BL to PTW12 (SD)	N	BL Mean	PTW12 Visit Mean	Mean Change from BL to PTW12 (SD)
FibroTest score	172	0.80	0.69	-0.11(0.101)	140	0.81	0.67	-0.13 (0.131)
INR	197	1.076	1.080	0.004 (0.1297)	166	1.048	1.071	0.023 (0.0996)
Albumin (g/L)	205	39.2	41.2	2.0 (2.80)	166	39.3	41.9	2.6 (3.17)
Platelet count ($x10^9$/L)	202	151.2	155.2	4.0 (33.72)	164	151.1	159.3	8.2 (34.09)
AFP (ng/mL)	202	16.424	5.697	-10.727 (15.6375)	105	20.715	4.900	-15.815 (26.4846)