Poster PS084

Non-invasive markers of liver fibrosis

Friday 15 April 16:45

Hall 8.0 B3

Liver fibrosis evaluation using real-time shear wave elastography: applicability, association with activity and steatosis, and diagnostic performance. Direct comparisons with transient elastography using biomarkers as reference.

Poynard, et al. France

Background and Aims: Real-time shear wave elastography (2D-SWE) is a two-dimensional transient elastography and a competitor as a biomarker of liver fibrosis in comparison with the standard reference transient elastography (TE). Unmet needs were the definition of applicability criteria (failure and reliability) for results' interpretation and assessments of the impact of inflammation (necrotico-inflammatory activity [A] and steatosis [S] on elasticity. The aims were in a large population to compare several criteria of applicability recently published, and to assess A and S impact on elasticity values.

Methods: We took FibroTest as a reference to compare the strength of concordance (Lin concordance coefficient [LCC] with fibrosis severity, between 2D-SWE, TE by M probe (TE-M) and by XL probe (TE-XL) after standardization of the different estimates. Validated ActiTest and SteatoTest were used as quantitative estimates of A and S severity, in order to assess their impact on elasticity independently of fibrosis severity presumed by FibroTest.

Results: A total of 2251 patients (pts) were included (37% CHC, 22% CHB, 27% NAFLD, 4% ALD, 9% Others). We validated the predetermined 0.2 kPa cut-off as a too low minimal elasticity value identifying not-reliable 2D-SWE results (LCC with FibroTest = 0.0281[-0.119; 0.175]). We were not able to identify discriminating cutoffs using variation-coefficient, BMI and depth of measures. The applicability of 2D-SWE (89.6%; 95%CI (88.2-90.8)) was significantly higher than that of TE-M (85.6%;84.0-87.0) and not different than that of TE-XL (88.2%; 86.8-89). In pts with non-advanced fibrosis (METAVIR F0F1F2), elasticity estimated by 2D-SWE was less impacted (LCC) by A and S than elasticity estimated by TEM: 0.039 (0.021; 0.058) vs. 0.090 (0.068; 0.112; $p < 0.01$) and 0.105 (0.068; 0.141) vs. 0.192 (0.153; 0.230; $p < 0.01$) respectively. The curve fitting, the univariate and the multivariate analyses clearly demonstrated that A and S increased elasticity, but A increased more the elasticity value than S, whatever the elastography method or the S measure evaluated for the first time by two non-invasive tests (SteatoTest or CAP).(Al lp-values <0.01)

Conclusions: 2D-SWE had a higher applicability than TE-M the reference elastography, with less impact of necro-inflammatory activity and steatosis especially in pts with non-advanced fibrosis, as presumed by blood tests. Elasticity results including very low minimal signal in the region of interest should be considered as not reliable.

Poster PS111

Fatty liver disease

Clinical

Saturday 16 April 13:00

Hall 8.0 A1

A post-hoc analysis of the GOLDEN505 trial demonstrates histological and cardiometabolic efficacy of Elafibranor-120 mg in patients with moderate or severe NASH that are eligible for pharmacotherapy

Ratziu et al. France.

Background and Aims: The GOLDEN505 randomized controlled trial of elafibranor (ELA) in NASH demonstrated overall histological efficacy of the 120 mg dose in the intention to treat population of 274 patients (pts). However participants had a wide range of disease severity with a strong placebo (PLB) response in mild NASH (baseline NAS, bNAS of 3) and a strong center effect due to inclusion of less than 3 pts in many centers. We performed a post-hoc analysis in order to reproduce eligibility criteria for future phase 3 trials and control for an unbalanced treatment distribution

Methods: Pts with mild/moderate NASH (bNAS ≥4) from centers that randomized at least one pt in each treatment arm (N = 120) were included. The primary end-point was reversal of NASH without worsening of fibrosis (ballooning score = 0 and with lobular inflammation score = 0-1) and no increase in fibrosis stage.

Results: ELA significantly increased the rate of resolution of NASH without worsening of fibrosis (26% vs. 5% in PLB, p = 0.02), the proportion of pts with a >2-point reduction in NAS (48% vs. 21% in PLB; p = 0.01) and decreased mean NAS (-1.1 vs. -0.38 in PLB; p = 0.02). These effects were mainly driven by a >1 grade reduction in ballooning (45% vs. 23% in PLB; p = 0.02) and lobular inflammation (55% vs. 33% in Pbo; p = 0.05) with a reduction in the mean ballooning score of -0.45 vs. -0.15 in PLB (p = 0.01), and inflammation score of -0.52 vs. -0.26 in PLB (NS). Steatosis was reduced (35% vs. 18% in PLB, NS) with steatosis score change of -0.13 vs. +0.03 in PLB (NS). Compared to PLB (effect-size), ELA improved liver tests: GGT (-29 UI, p <0.001), ALT (-18 UI, p <0.01), ALP (-20, p <0.001); and the lipid profile: TG (-0.66 mmol/L, p <0.01), total-Cholesterol (-0.45 mmol/L, p <0.05), non-HDL-C (-0.54 mmol/L, p <0.01), HDL-C (+0.12 mmol/L, p <0.05) and LDL-C (-0.18 mmol/L). Glucose homeostasis and inflammation markers were also improved. Non-invasive fibrosis scores were reduced: Fibrotest (p <0.05) and NAFLD fibrosis score (p <0.01).

Conclusions: In the target population of pts with moderate/severe NASH (bNAS >4) that are eligible for pharmacotherapy in clinical practice and for inclusion in phase 3 trials, ELA induced resolution of NASH without worsening of fibrosis in a quarter of pts and histological improvement in half of them. This was driven by significant effects on hepatocyte ballooning and lobular inflammation. ELA-treated patients improved the global cardiometabolic risk profile

Saturday Poster Session

P 486

Spectrum of NAFLD severity in a large population using software-combined tests of steatosis (S), necroinflammatory activity (A), and fibrosis (F) (FibroMax) in comparison with patients with chronic hepatitis C (CHC)

Poynard et al. France

Background and Aims: Among patients (pts) with NAFLD, the severity of main features, S, A, and F (SAF), as well as their respective associations with age and gender, have been estimated as per biopsy in a very limited number of patients, in comparison with CHC.

We aimed to determine the spectrum of "SAF" severity in a centralized database of NAFLD pts consecutively investigated by validated biomarkers of S (SteatoTest), A (ActiTest [AT]) and F (FibroTest). We also assessed the variability of transaminases ALT, often used as a simple marker of severity, according to gender and age.

Methods: From 2005 to 2014, FibroTest, ActiTest and SteatoTest were performed in 37,315 pts with NAFLD, and FibroTest-ActiTest in 252,688 pts with CHC in a centralized USA lab using standardized pre-analytical and analytical methods. We analyzed (R software) the SAF scores,(METAVIR-equivalent) as well as the cirrhosis severity by predetermined categories (J Hepatol 2014: F4.1 (compensated), F4.2 (compensated + bleeding risk), F4.3 (decompensated), according to birth-year, and gender.

Results: Female gender was more frequent in NAFLD (55.9%) than in CHC (32.9%), with similar median (SD) age, 53.9yr (14) vs 53.0yr (12), but with less pts born between 1945-1965 (baby boomers: 57.5% vs 70.4%) and twice more born before 1945 (17.1% vs 8.3%). Severity was lower in NAFLD vs CHC, less F3F4 14.2% vs 32.9%, less F2-A2A3 1.6% vs 3.1%, less F2-A0A1 4.0% vs 6.7%, more F0F1-A2A3 10.6% vs7.8% and more F0F1 69.6% vs 49.5%, and among F4 more F4.1 54% vs 47%. In multivariate regression, taking into account age and gender, the risk (oddsratio [95%CI]) of F3F4 was still lower in NAFLD than in CHC = 0.33[95% CI: 0.32-0.34]), as well as for A2A3 (0.59[0.57- 0.60]). Among NAFLD, F3F4 was associated positively with activity severity (134 [114-157]) and negatively with steatosis (-28[-23;-3.3]); severe steatosis (grade S3 >32%) was negatively associated with male gender (0.90[0.87-0.94]). In male median ALT decreased dramatically with age, from 75 IU/L (year-1990) to 50 IU/L (year-1950)(All previous differences P<0.0001) and not in women (stable at 50 IU/L), both in NAFLD and CHC, precluding ALT use as a component of fibrosis panels such as FIB4.

Conclusions: In patients with NAFLD, the proportion of severe fibrosis presumed by FibroTest, was three times lower compared with patients with CHC, after taking into account age and gender. In males, ALT (directly or in scores) cannot not be used as a severity biomarker either in NAFLD or in CHC.

GS13
General Session 3

Saturday 16 April
08:30

Cirrhosis determined with FibroTest in IFN-free regimen trial HCV infected kidney transplant recipients

Ledipasvir/Sofosbuvir for 12 or 24 weeks is safe and effective in kidney transplant recipients with chronic genotype 1 or 4 HCV infection

Colombo et al. Milan.

Background and Aims: Interferon (IFN) and ribavirin (RBV) for the treatment of chronic hepatitis C (HCV) in kidney transplant recipients is complicated by the risk of the allograft rejection and poor tolerability. We evaluated the safety and efficacy of the IFN-free, RBV-free regimen of ledipasvir/sofosbuvir (LDV/SOF) in chronic genotype (GT) 1 or 4 HCV infected kidney transplant recipients.

Methods: Kidney transplant recipients with chronic GT1 or GT4 HCV infection, treatment-naïve and treatment-experienced, with or without compensated cirrhosis were randomized 1:1 at 5 sites in Europe to receive LDV/SOF (90 mg/400 mg) for 12 or 24 weeks. Randomization was stratified by HCV genotype, treatment history and presence or absence of cirrhosis. Cirrhosis was determined by liver biopsy (Metavir score = 4 or Ishak score ≥5), Fibroscan® >12.5 kPa, or Fibrotest® >0.75 and APRI >2. A pretreatment creatinine clearance <40 ml/min was an exclusionary criterion. The primary endpoint was SVR12.

Results: 114 patients were randomized and treated; median age was 53, 58% were male, 94% were white, 72% carried the non-CC IL28B allele, 91% had genotype 1 infection, 69% were treatment-naïve, and 15% had compensated cirrhosis. The median eGFR was 56 ml/min (range 35-135 ml/min). All 92 patients with SVR4 data available achieved SVR4 including a patient discontinuing treatment at Week 4 due to an AE. SAEs were reported in 12 (11%) patients; 3 were assessed as treatment related: syncope, pulmonary embolism, and blood creatinine increased. The most frequent AEs were headache (19%), asthenia (13%), and fatigue (10%).

Conclusions: Administration of LDV/SOF for 12 or 24 weeks in patients with chronic HCV genotype 1 or 4 patients who have undergone kidney transplant was safe and highly effective with an SVR4 rate of 100%. Treatment was well-tolerated. SVR12 data for all patients will be presented.