

LateBreaker
ePOSTER
LP41

Fibrosis Epidemiology with FibroTest

LIVER FIBROSIS EPIDEMIOLOGY REVISITED USING SOFTWARE
COMBINED BIOMARKER: PROOF OF CONCEPT USING 1,081,658
CENTRALIZED FIBROTEST (FT) PRESCRIPTIONS.

Poynard, et al. France

Introduction: The epidemiology of liver fibrosis (LF) was classically described by liver biopsy (LB), therefore limited by bias of LB indication and sample size. Several LF biomarkers have been validated including FibroTest (AIM 2013). We aimed to revisit the epidemiology of LF using the centralized software combined database (DB) of FibroTest, for assessing the impact of age and sex on LF severity (LFS) as well as the impact of health policy for screening LFS.

Material and Methods: From 2002 to 2014, 1,081,658 interpretable FibroTest, were performed consecutively on fresh serum, mostly for chronic hepatitis C (CHC). In 5 countries, France (Fr), USA, Romania (Ro), Egypt (Eg) and Morocco (Ma), we compare (R software): LFS (METAVIR scoring system F0 to F4 and cirrhosis severity F4.1 compensated, F4.2 bleeding risk and F4.3 complicated, J Hepatol 2014), the density of LFS according to birth-year (BY) and sex, and the progression of FibroTest dissemination. We used as controls a DB of CHC with LB (Lancet 1997 n=2235, Gastro 2002 n=4177).

Results: F4 prevalence varied from 13.8% (Ro), 14.9% (Fr), 18.1% (USA), 22.1% (Ma) to 28.2% (Eg). In France, FibroTest was commonly prescribed, with stable rates since reimbursement (2006); a high number of F4 was detected in women born before 1945 (n=20,672). In USA, FibroTest (FibroSure) rate dramatically increased in 2013-2014 when the baby-boomer campaign (BY 1945-1965) started, vs 2011-2012 (+132%). In multivariate regression analysis, adjusted for age (OR=1.06) and sex (OR=3.22) and USA as reference (OR=1), Eg had the higher risk (OR=2.3; 2.2-2.3) possibly due to associated schistosomiasis; then Ma (OR=1.3; 1.2-1.3) and Ro (1.1; 1.1-1.2; masked in univariate (younger age) and lower risk for Fr (0.90; 0.88-0.91); All P<105. Sensitivity analyses (excluding age-sex- FibroTest standardization, repeated FibroTest, non-CHC) observed similar results. Associations between LFS age and sex were similar in LB-DB. Figure: Density of LFS, according to BY and sex, in Fr (n=513,762), USA (263,422), Ro (49,812), Eg (34,168) and Ma (16,542). Blue (men) and red lines (women) were regression lines LF/age; vertical black lines were 1945-1965 cutoffs, concentric black lines were density-10percentiles.

Conclusions: Despite possible bias associated with patented biomarker prescription, this proof-of-concept study permitted already to prepare better strategies to reduce the burden of cirrhosis, based on 200 times more patients than biopsy. The first interpretation for France is to prevent without delay a massive burden of death in women born before 1945.

ePOSTER
P0510

Compared performances of FibroTest, Transient Elastography, APRI and Fib-4 using Bayesian Methods

Direct comparisons of FibroTest, APRI, FIB-4, and transient elastography (TE) for the diagnosis of cirrhosis and fibrosis, in patients with chronic hepatitis C (CHC) and B (CHB) using intention to diagnose and bayesian methods. a systematic review

M. Houot et al. France.

Background and Aims: The diagnostic performances of noninvasive tests for the diagnosis of cirrhosis (F4) or clinically significant fibrosis (METAVIR stages F2F3F4) in chronic liver disease (CLD) have been assessed using indirect comparisons and "per-protocol" (PP) analysis, that is, without taking into account the applicability (failure or non reliability) of tests, ["intention-to-diagnose" (ITD)]. As for drugs, indirect comparisons between tests are limited by the spectrum effect and PP analysis by applicability effect. The aim was to compare the performance of the four most validated tests (FibroTest, TE, APRI and FIB-4) in patients with chronic liver diseases using only direct comparison, ITD and Bayesian methods.

Methods: Direct comparisons using biopsy as reference were searched (MEDLINE) from 2001 to 2014; four methods were used for AUROCs' difference (AUC-D) in ITD: the descriptive AUC-D (Chou 2013), pooled indirect AUC-D, pooled direct AUC-D and pooled direct Bayesian AUC-D (BayesAUC-D).

Results: Among 1279 biomarker studies identified, 71 studies with 77 groups of patients were included (37 with CHC only, 28 CHB only, and 12 "MixedCB" defined as CHC-CHB >49% of CLD) allowing 185 direct comparisons between the 4 tests' AUROCs; 99 for F2F3F4 (12,725 patients) and 86 for F4 (10,929 patients). The significant (credibility interval) BayesAUC-D were 0.06 in favor of FibroTest vs TE and 0.05 vs APRI; for cirrhosis BayesAUC-D were 0.07 in favor of TE vs APRI and 0.04 for FIB4 vs APRI. Non-applicability rate (median/range) was 0% (0-8%) for FibroTest lower ($P < 0.0001$) than for TE 8% (0-41.8); APRI and FIB4 have no rules for applicability.

Conclusions: This overview, the first focusing on direct comparisons in ITD and using Bayesian meta-analysis, permitted to compare fibrosis biomarkers without the limitations of metaanalyses not taking into account the tests' applicability, and of indirect comparisons. FibroTest had better performance than TE for the diagnosis of F2F3F4, in CHC and CHB, which was not observed by indirect and per-protocol previous meta-analyses.

Oral
communication
0017

Modelisation to Predict 5-Years (yr) Incidence of Cirrhosis/Death in France, Italy and UK

EFFECTIVENESS OF TREATMENT INITIATION BASED ON FIBROSIS STAGE ASSESSED BY METHODS OF FIBROSIS DIAGNOSIS IN TERMS OF 5-YEAR INCIDENCE OF MORBI-MORTALITY

S. Deuffic-Burban et al. France

Background and Aims: European and American experts recommend targeting HCV antiviral therapy to patients (pts) with fibrosis \geq F2, with the highest priority assigned for F3–F4. The impact of targeted therapy has never been evaluated in light of the risk of misclassification of the methods of fibrosis diagnosis.

Methods: A country-specific decision model was used to predict 5-year (yr) incidence of cirrhosis and deaths in three countries with different profiles of natural history (France, Italy, UK). Fibrosis misclassification was integrated for different methods: liver biopsy (LB), fibroscan (FS), patented scores (FibroTest, hepascore, fibrometer), and APRI. IFN-free regimens were initiated considering two scenarios where pts are distributed in fibrosis stage \geq F2 (F2-scenario) and \geq F3 (F3-scenario), according to available thresholds of methods. Outcomes based on the use of these methods were compared to those using a perfect staging (no misclassification) and a random distribution (50% of pts were considered for therapy regardless of fibrosis stage).

Results: In F2-scenario, 5-yr incidence of cirrhosis is: 0.2–1.3% using the perfect staging, 0.3–2.6% with LB, 0.4–3.7% with FS, 0.3–3.2% with patented scores, 0.4–4.1% with APRI-0.5, 0.9–8.7% with APRI-1.5, 0.6–5.6% with random distribution; 5-yr incidence of deaths is: 0.3–1.2% using the perfect staging, 0.3–1.3% with LB, 0.3–1.4% with FS, 0.3–1.4% with patented score, 0.4–1.6% with APRI-0.5, 0.8–3.1% with APRI-1.5, 0.7–2.7% with random distribution. In F3-scenario, using the perfect staging, 5-yr incidence of cirrhosis increases dramatically, at least for France and Italy, whereas this scenario has less impact on 5-yr incidence of liver deaths; using methods of diagnosis and due to their risk of misclassification, 5-yr incidence of cirrhosis shows 28–60% relative increase compared to F2-scenario in France and Italy, whereas the increase is lower in UK, as well as 5-yr incidence of liver deaths.

Conclusions: Based on the unrealistic scenario of perfect staging, F2- and F3-scenarios are efficient to reduce 5-yr incidence of liver-related deaths but F3-scenario is not optimal in terms of 5-yr incidence of cirrhosis. LB, FS and patented scores are efficient to select subgroups with higher risks of cirrhosis and mortality: F2- and F3-scenarios are still efficient in terms of 5-yr incidence of mortality although their impact would be lower than perfect-staging; conversely, they are associated with deleterious impact on 5-yr incidence of cirrhosis, mainly F3-scenario.

ePOSTER
P1036

FibroMax for Screening Risk Factors Influencing the Outcome in NAFLD Patients

Obesity, T2DM, metabolic syndrome influence mortality

in NAFLD in a cohort of Mexican patients

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Background and Aims: The spectrum of non alcoholic fatty liver disease (NAFLD) comprises non alcoholic fatty liver (NAFL), non alcoholic steatohepatitis (NASH) and cirrhosis. Recently, it has been positioning as one of the most frequent causes of chronic liver disease (CLD). Mexico has the second highest worldwide prevalence of obesity and type 2 diabetes mellitus (T2DM) is present in 14% of general population. The aim of this study was to evaluate the influence that metabolic factors had in the natural history of NAFLD in Mexican patients.

Methods: NAFLD diagnosis was made in patients who drank <30 g/day on males, <20 g/day on females. Other etiologies of CLD were ruled out. Demographic, anthropometric, biochemical, US data and comorbidities were registered. All patients had liver biopsy and/or FibroMax. Group 1 (G1): 41 NAFL patients and group 2 (G2): 80 NASH patients. Comorbidities were compared between admission and last visit. Kaplan–Meier curves (KM) were calculated evaluating the development of cirrhosis, its complications and mortality or liver transplant (LT).

Results: During follow-up obesity decreased in both groups, however HBP increased significantly in G1 as T2DM, HBP, dyslipidemia and metabolic syndrome (MS) increased in G2 (Table). Forty patients had cirrhosis initially, and in G2 four patients developed it. Cirrhosis was diagnosed in 44/121 (36%) patients. Twelve out of 121 (10%) patients died/LT, 11 of them were cirrhotic. Causes of death: liver related 9/12 (75%), cardiovascular causes 2/12 (17%) and infection 1/12 (8%). KM curves demonstrated that patients with obesity ($p = 0.041$), T2DM ($p = 0.002$) and metabolic syndrome ($p = 0.001$) had higher mortality/LT. The development of cirrhosis during follow-up was not influenced by comorbidities.

Conclusions: Patients with NASH developed more comorbidities than patients with NAFL in the long term follow-up. Patients with obesity, T2DM and MS had higher mortality/LT. However the development of cirrhosis during follow-up was not influenced by comorbidities. The most common cause of death in NAFLD was liver related.

ePOSTER
P0782

FibroTest for Cirrhosis and Fibrosis Assessment in DAA Phase 3 trial (ALLY-3 Study)

ALL-ORAL 12-WEEK COMBINATION TREATMENT WITH DACLATASVIR (DCV) AND SOFOSBUVIR (SOF) IN TREATMENT-EXPERIENCED PATIENTS INFECTED WITH HCV GENOTYPE (GT) 3: A SUBANALYSIS OF THE ALLY-3 PHASE 3 STUDY

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Background and Aims: The phase 3 ALLY-3 study evaluated the all-oral, ribavirin (RBV)-free combination of daclatasvir (DCV; pangenotypic NS5A inhibitor) and sofosbuvir (SOF; NS5B polymerase inhibitor) in patients with GT3 infection. After 12 weeks of treatment, sustained virologic response at posttreatment Week 12 (SVR12) was achieved by 90% and 86% of treatment-naïve and -experienced patients, respectively. **Methods:** Treatment-naïve (N = 101) and experienced (N = 51) patients received open-label DCV 60mg + SOF 400mg once daily for 12 weeks. This subanalysis provides further details of efficacy and safety outcomes in the experienced cohort.

Results: Treatment-experienced patients were predominantly male (63%), white (88%) and non-cirrhotic (67%); 75% had baseline HCVRNA ≥ 800 IU/mL, and 61% had non-CC IL28B genotypes. Patients had previously received IFN-based (n = 42), SOF-containing (n = 7, including 7 treated with SOF/RBV and 1 who was retreated with SOF/peg/RBV) and alisporivir-containing (n = 2) regimens. Prior responses included relapse (n = 31), null response (n = 7), partial response (n = 2), and other forms of nonresponse or IFN intolerance (n = 11). All patients completed 12 weeks of study treatment. SVR12 was achieved in 44 patients (86%); all prior null and partial responders, and IFN-intolerant patients achieved SVR12. SVR12 rates were higher in patients without cirrhosis and in those with IL28B CC genotype (Table). Treatment failure (relapse) was experienced by 7 patients, including 5 prior IFN/RBV recipients (prior response: relapsers, n = 4; HCVRNA never undetectable, n = 1) and 2 patients who relapsed after prior treatment with SOF/RBV. Of the two prior SOF relapsers, one had cirrhosis with grade 1 steatosis, and one had Fibrotest F3 with grade 2 steatosis, and a baseline NS5A-Y93 resistance-associated variant. There were no serious AEs or AEs leading to discontinuation. Grade 3/4 AEs (a single report of arthralgia) and grade 3/4 lab abnormalities (platelets, n = 1; lipase, n = 1) were uncommon. The most frequent AEs (any grade) were fatigue (26%), headache (20%), nausea (14%) and arthralgia (12%). Safety parameters were similar in those with or without cirrhosis.

Conclusions: This all-oral, 12-week combination of DCV+SOF achieved high SVR12 rates in GT3 patients previously treated with all oral DAA or IFN-containing regimens. DCV+SOF was well tolerated.

P0808

Improvement of FibroTest in Cirrhosis with SVR from Phase 3 TURQUOISE-II Trial.

IMPROVEMENT IN LIVER FUNCTION AND NON-INVASIVE ESTIMATES OF LIVER FIBROSIS 48 WEEKS AFTER TREATMENT WITH OMBITASVIR/PARITAPREVIR/R, DASABUVIR AND RIBAVIRIN IN HCV GENOTYPE I PATIENTS WITH CIRRHOSIS

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Background and Aims: Viral eradication in individuals with chronic HCV infection and cirrhosis may result in improvement in hepatic synthetic function and reduce portal hypertension. The interferon-free 3 direct-acting antiviral (3D) regimen of ombitasvir, paritaprevir (identified by AbbVie and Enanta, dosed with ritonavir [r]), and dasabuvir with ribavirin (RBV) has shown high rates of sustained virologic response rates 12 weeks post-treatment

Methods: In this open-label trial, patients were randomized to receive 3D + RBV for 12 or 24 weeks. Changes in non-invasive estimates of liver fibrosis [AST to platelet ratio (APRI), FIB-4, Forns Index, FibroTest], laboratory surrogates for hepatic synthetic function [international normalized ratio (INR), albumin, platelet count], and alpha fetoprotein (AFP) levels were measured over time.

Results: Among 380 patients randomized to 12 or 24 weeks of 3D + RBV, SVR12 rates were 92% and 97%, respectively. In general, mean non-invasive estimates of liver fibrosis, surrogates for hepatic synthetic function, and AFP improved from baseline to post-treatment week 12 (PTW12), and further improved by posttreatment week 48 (PTW48; Table). In patients treated for 12 and 24 weeks who achieved an SVR12, mean FibroTest scores improved to 0.64 and 0.65 at PTW48, respectively. Conversely, in patients who did not achieve SVR12 after 12 and 24 week treatment, mean FibroTest scores increased to 0.89 and 0.89, respectively. Results by baseline disease severity will be presented.

Conclusions: In the phase 3 TURQUOISE-II trial of patients with HCV genotype I and cirrhosis, treatment with the 3D + RBV regimen improved surrogates of hepatic synthetic function, AFP levels, and FibroTest scores after completion of antiviral therapy in patients with HCV genotype I infection and cirrhosis.

P0842

FibroTest to Exclude Cirrhosis in DAA trial (MALACHITE-I)

MALACHITE-I: PHASE 3B TRIAL OF OMBITASVIR/PARITAPREVIR/R AND DASABUVIR +/- RIBAVIRIN OR TELAPREVIR + PEGINTERFERON/RIBAVIRIN IN TREATMENT-NAIVE ADULTS WITH HCV GENOTYPE 1.

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Background and Aims: In phase 3 trials, regimens of coformulated ombitasvir/paritaprevir/r (paritaprevir [formerly ABT-450] identified by AbbVie and Enanta, co-dosed with ritonavir [r]) and dasabuvir +/- ribavirin (3D±RBV) demonstrated high efficacy rates and low rates of drug discontinuation due to adverse events (AEs) in patients with chronic HCV genotype (GT) 1 infection. Telaprevir (TPV) plus peginterferon (pegIFN)/RBV remains the standard of care for chronic HCV GT1 infection in many regions. However, this regimen is associated with long treatment duration, suboptimal efficacy, and treatment-limiting AEs related to pegIFN/RBV and exacerbated by TPV-associated rash and anemia. MALACHITE-I is the first multicenter trial to directly compare efficacy and safety of an all-oral direct-acting antiviral regimen (3D±RBV) and TPV+pegIFN/RBV in treatment-naive HCV GT1-infected pts without cirrhosis.

Methods: This multicenter, open-label trial included 311 HCV GT1-infected treatment-naive patients without cirrhosis. Patients received 3D+RBV for 12 weeks, 3D for 12 weeks, or TPV+pegIFN/RBV for 12 weeks and pegIFN/RBV for an additional 12–36 weeks (total treatment duration of 24–48 weeks). Patients with GT1a infection were randomized 2:1 to 3D+RBV and TPV+pegIFN/RBV. Patients with GT1b infection were randomized 2:2:1 to 3D+RBV, 3D, and TPV+pegIFN/RBV. The primary endpoint was SVR12. Patients will be followed for 48 weeks post-treatment.

Results: Patient baseline characteristics are in Table 1. For patients receiving 3D+RBV or 3D, SVR4 and SVR12 rates were 97.1–98.8%; 3 patients had on-treatment failure and 1 patient had post-treatment relapse (Table 1). SVR4 rates were 82.9–85.3% for patients receiving TPV+pegIFN/RBV; SVR12 rates for the TPV+pegIFN/RBV arm will be presented. Rates of common AEs (including anemia, nausea, and pruritus), AEs leading to drug discontinuation or RBV dose modification, and serious AEs were significantly lower in patients receiving 3D±RBV compared to patients receiving TPV+pegIFN/RBV (Table 2). The frequency of RBV-associated AEs, such as anemia, was significantly lower in the 3D±RBV arms compared to the TPV+pegIFN/RBV arm.

Conclusions: In this trial, 12 weeks of 3D±RBV resulted in SVR12 rates of 97.1–98.8% while 12 weeks of TPV with 24–48 weeks of pegIFN/RBV resulted in SVR4 rates of 82.9–85.3% in treatment-naive patients with chronic HCV GT1 infection without cirrhosis. 3D±RBV also demonstrated better tolerability, with ≤0.7% of patients experiencing an AE leading to treatment discontinuation.

ePOSTER P0887

FibroTest to diagnose cirrhotics and non-cirrhotics among subjects co-infected with HIV and HCV in Phase III study using DAA

C-EDGE CO-INFECTED: PHASE 3 STUDY OF GRAZOPREVIR/ ELBASVIR IN PATIENTS WITH HCV/HIV.

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Background and Aims: The combination of grazoprevir (GZR, MK- 5172, a HCV NS3/4 protease inhibitor) and elbasvir (EBR, MK-8742, an HCV NS5A inhibitor), an interferon-free, ribavirin-free, oncedaily, fixed-dose combination (FDC) tablet has demonstrated robust efficacy and an excellent safety profile in diverse populations. C-EDGE HIV/HCV is an ongoing, phase III study to assess the safety and efficacy of GZR/EBR FDC in HIV co-infected patients with chronic HCV genotype (GT) 1, 4 or 6 infection, with or without cirrhosis.

Methods: Subjects were eligible for enrollment if they met all of the following criteria: chronic HCV GT 1, 4 or 6 infection, cirrhotic or non-cirrhotic, no prior HCV treatment, HIV infection on a stable antiretroviral (ARV) regimen with a CD4 >200 cells/mm³ and an HIVRNA <20 copies/mL, or HIV-treatment naive with CD4 >500 cells/mm³ and VL <50,000 copies/mL. ARV therapy included a dual NRTI of tenofovir or abacavir, and lamivudine or emtricitabine; and either raltegravir, dolutegravir or rilpivirine. Presence of cirrhosis was defined by either (1) histology, (2) fibroscan >12.5 kPa, or (3) fibrotest >0.75 and APRI >2.0. All patients received open label GZR/EBR 100 mg/50mg FDC QD for 12 weeks. The primary endpoints were sustained virologic response (SVR) at follow-up week 12 (COBAS TaqMan v2.0 [lower limit of quantitation <15 IU/mL]), and assessment of safety and tolerability.

Results: 262 subjects were screened and 218 subjects met criteria for enrollment. Table 1 displays baseline characteristics for the enrolled subjects. In preliminary results among 214 subjects for whom HCV RNA data was available, 212 (97%) achieved SVR4. Virologic failure occurred in 2/218 (0.9%); both categorized as relapses at FW4. Overall adverse events (AEs) were reported in 157/218 subjects (72%); drug-related adverse events occurred in 72/218 subjects (33%); serious AEs occurred in 2/218 subjects (0.9%). The most common AEs reported included fatigue (15%), headache (15%), nausea (10%), diarrhea (10%), and insomnia (9%). Through FW4, no patient has discontinued due to AEs or laboratory abnormalities. Two patients experienced transient HIV viremia (HIV RNA >200 copies/mL); both patients were subsequently undetectable.

Conclusions: This is a large, ongoing, Phase III study among subjects co-infected with HIV and HCV GT 1, 4 or 6 including significant numbers of Black/African-American and cirrhotic patients. A 12-week regimen of GZR/EBR FDC was highly efficacious with respect to SVR4 among cirrhotic and non-cirrhotic HIV co-infected subjects with HCV GT 1, 4 or 6 infection, and has a favorable safety profile. SVR12 results will be presented at the ILC meeting.