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HIGH-RESOLUTION HCV SUBTYPING USING MASSIVE SEQUENCING AND PHYLOGENY, OPTIMAL ALTERNATIVE TO CURRENT METHODS

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Background and Aims: HCV is classified into seven major genotypes (G1-G7) and at least 67 subtypes, within the genotypes. Recent studies suggest that subtyping will become an important predictor of antiviral response, especially in new treatments with Direct Antiviral Agents in IFN-free regimens in which Sustained Virological Response (SVR) rates may differ between 7% and 45%. Current commercial available methods are capable of genotyping, but its subtyping capacity is somehow limited.

Methods: We have developed a High-resolution HCV subtyping using 454/GS-Junior and compared, in a group of well-pedigreed samples (82 genotype 1 and 32 non-1 untyped samples by first-generation LiPA), with commercial Versant/Siemens and Real-time PCR/Abbott methods, using direct-PCR Sanger sequencing as a reference method.

Results: Absolute concordance was obtained between High-resolution HCV subtyping and Sanger for subtypes 1a and 1b samples. The subtype could not be established in 16% of genotype 1 samples (13/82) by either Versant/Siemens and Rt-PCR/Abbott. Interestingly, one sample which was classified as 1b by Direct-PCR Sanger sequencing and by both commercial techniques, had a mixed infection of HCV subtypes, 1b (43%)+3a (35%)+1a (22%) by High-resolution HCV subtyping.

Among the 32 non-1 untyped samples, absolute concordance was found between Sanger and High-resolution HCV subtyping except in four samples in which mixed infection was observed. The two commercial available genotyping methods used, were unable to identify the HCV subtype of the majority of these samples.

Conclusions: High resolution HCV subtyping of chronic HCV patients entering new DAA regimens, will help discover the real rate of SVR associated with treatment regimen and HCV subtype.

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ANRS HC15 NRFI: LONG-TERM MAINTENANCE THERAPY WITH A COMBINATION OF RIBAVIRIN AND PEGYLATED INTERFERON IN CHRONIC HEPATITIS C. RESULTS OF A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Background and Aims: Severe fibrosis is responsible for the mortality associated with chronic hepatitis C infection. Long-term maintenance therapy using low-dose pegylated interferon (pegIFN) was unable to reduce the progression of fibrosis and the rate of hepatic complications in the pivotal Halt-C trial.

The aim of the study was to assess the efficacy of a combination of ribavirin (RBV) and low-dose PegIFN on fibrosis in non responders to previous PegIFN-RBV treatment.

Methods: 372 patients with METAVIR Fibrosis score ≥ 2 were included and treated with 0.5 µg/kg/week alpha2b-PegIFN during 3 years. They were randomized (stratification on cirrhosis) between two groups treated with RBV (n = 186; 800–1200 mg/d depending on body weight) or placebo (n = 186). Fibrosis was histologically assessed before and after treatment and using elastography (Fibroscan®) every 12 months. Patients were monitored for the occurrence of severe hepatic events: hepatocellular carcinoma (HCC), hepatic decompensation and liver-related death.

Results: At baseline, the 2 groups did not differ considering age (54±10 yr), gender (65% male), genotype 1 (81%), prevalence of cirrhosis (54%) or oesophageal varices (30% of cirrhotics). The RBV group encountered a greater decrease of haemoglobin between baseline and end of treatment (−2.2±1.5 versus −0.9±1.1 g/dl) but the overall tolerance was satisfying with similar rates of treatment discontinuation in both groups. The table shows the results obtained.

Table (abstract P1111).

	RBV + PegIFN (n = 186)	Placebo + PegIFN (n = 186)	p value
Study completion [n (%)]	157 (84.4%)	154 (82.8%)	0.674
Treatment discontinuation [n (%)]	71 (38.2%)	78 (42.2%)	0.433
Treatment duration (months)	28.7±11.4	28.1±11.4	0.639
Severe hepatic event [n (%)]	18 (9.7%)	9 (4.8%)	0.072
Hepatocellular carcinoma [n (%)]	14 (7.5%)	5 (2.7%)	0.034
Serum ALAT (UI/l)*	−48±81 UI/l	−8±68 UI/l	<0.001
Serum Ferritin (µg/l)*	353±527	86±402	<0.001
Evolution of activity (Metavir)* (%improve/stable/increase)	(44.8%/43.4%/11.9%)	(22.1%/64.1%/13.7%)	<0.001
Evolution of fibrosis (Metavir)* (%improve/stable/increase)	(11.5%/58%/30.5%)	(14.8%/57.8%/27.3%)	0.764

* Difference between baseline and end-of-treatment.

Conclusions: Despite a better effect on inflammation and elasticity, the addition of RBV to PegIFN did not induce any beneficial effect on liver fibrosis score. Moreover, an increase of serum ferritin and a higher prevalence of HCC were observed.

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LONG TERM FOLLOW-UP OF PATIENTS TREATED WITH SOFOSBUVIR IN THE FISSION, POSITRON, FUSION AND NEUTRINO PHASE 3 STUDIES

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Background and Aims: We report the results from an interim analysis of long term follow-up of patients who were treated with sofosbuvir (SOF)-based regimens in the Phase 3 Studies FISSION, POSITRON, FUSION and NEUTRINO.
Methods: Patients in the SOF Phase 3 studies who achieved SVR were offered enrollment in a SVR Registry and those who did not achieve SVR were offered enrollment in a Resistance Registry. Periodic laboratory evaluations, clinical assessment of liver disease, and quality of life assessments (SF-36) were performed for up to 3 years.
Results: 487 patients representing 65% of those eligible from the Phase 3 studies enrolled into the SVR Registry with a median (range) follow-up of 24 (1–49) weeks. 114 patients representing 52% of those eligible from the Phase 3 studies have enrolled in the Resistance Registry with median (range) follow-up of 25 (1–49) weeks. Demographic and disease characteristics of the populations in both studies are presented below. All patients in the SVR registry have maintained SVR through follow up. 60% of patients have discontinued from the Resistance Registry primarily due to the available of SOF-based re-treatment protocols for patients not achieving SVR in the Phase 3 studies. There were no significant changes in laboratory evaluations, liver disease assessments or SF-36 scores in either study. One patient had newly diagnosed hepatocellular carcinoma during the Resistance Registry.
Conclusions: This interim analysis indicates that SVR achieved with SOF-based treatment is durable. Further follow-up will be necessary to determine the impact of SVR or treatment failure on liver disease regression or progression.

Table: Demographics and disease characteristics

	SVR Registry (N = 487)	Resistance Registry (N = 114)
Age, years (range)	53 (20–76)	54 (28–67)
Male, n (%)	286 (59)	93 (82)
Cirrhosis, n (%)	85 (18)	41 (36)
Treatment experienced, n (%)	91 (19)	49 (43)
IL28B genotype, n (%)		
CC	175 (36)	38 (33)
CT	244 (50)	60 (53)
TT	68 (14)	16 (14)
HCV genotype, n (%)		
1	192 (39)	24 (21)
2	150 (31)	8 (7)
3	121 (26)	81 (71)
4	14 (3)	1 (<1)
6	3 (<1)	–

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CHOLESTEROL METABOLISM DURING PEG-IFN + RBV + TVR TREATMENT

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Background and Aims: Telaprevir (TVR) is an NS3/4A protease inhibitor that is used for the treatment for chronic HCV patients in combination with peg-IFN and ribavirin (RBV). HCV life cycle tightly correlates with lipids metabolism in hepatocytes, while little is known about the variation during the treatment and impact for the therapeutic effect of cholesterol metabolism.
Methods: The patients with HCV genotype 1b have been treated with peg-IFNα2b + RBV + TVR from 2011 (n = 119). We analyzed cholesterol kinetics during the treatment. The effects of TVR were examined on the expression of lipid metabolism-related genes in HepG2 cells using real-time RT-PCR.
Results: Serum total cholesterol and LDL cholesterol level were elevated drastically from early course of the treatment and normalized after the TVR usage for every patient. Serum total cholesterol and LDL cholesterol level before the treatment were higher in patients with SVR and serum cholesterol level was selected as an independent contribution factor for the SVR 24 weeks. Serum level and incretion from the beginning of treatment of total cholesterol were higher in patients with SVR during TVR adhibition. In HepG2 cells, TVR significantly suppressed the expression of LDL receptor that was involved in the entry of HCV to hepatocyte as well as the transcript of ACC1, FAS, and SREBP1c.
Conclusions: Here we showed TVR also had antiviral effect via inhibiting viral entry to the liver as well as inhibiting protease activity. Controlling lipid metabolism could be important for the HCV treatment using direct acting antiviral drugs.

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PATIENT-REPORTED OUTCOMES (PROS) IN CHRONIC HEPATITIS C PATIENTS WITH CIRRHOSIS TREATED WITH SOFOSBUVIR (SOF) CONTAINING REGIMENS

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Background and Aims: PROs are important to assess the full impact of anti-HCV treatment on patients' well-being. Whether presence of cirrhosis influences PROs with newly available regimens is important. Our aim was to compare PROs in patients with and without cirrhosis undergoing treatment with SOF-containing regimens.
Methods: PRO questionnaires [Short Form-36 (SF-36) Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), and Work Productivity and Activity Index (WPAI-SHP)] were administered to subjects receiving SOF+RBV (FUSION, N = 201, 34% cirrhosis) and SOF+RBV+IFN (NEUTRINO, N = 327, 17% cirrhosis).
Results: Cirrhotic patients treated with IFN-free regimen did not show significant decline in PROs (0%-3.9% of maximum possible