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Stanislas POL[1], Marc BOURLIERE[2], Sandy LUCIER[3], Christophe HEZODE[4], Céline DORIVAL[3], Dominique LARREY[5], Jean-Pierre BRONOWICKI[6], Victor DE LEDINGHEN[7], Fabien ZOULIM[8], Albert TRAN[9], Sophie METIVIER[10], Jean-Pierre ZARSKI[11], Didier SAMUEL[12], Dominique GUYADER[13], Patrick MARCELLIN[14], Anne MINELLO[15], Laurent ALRIC[16], Dominique THABUT[17], Olivier CHAZOUILLERES[18], Ghassan RIACHI[19], Valérie BOURCIER[20], Philippe MATHURIN[21], Véronique LOUSTAUD-RATTI[22], Louis D'ALTEROCHE[23], Isabelle FOUCHARD-HUBERT[24], François HABERSETZER[25], Xavier CAUSSE[26], Claire GEIST[27], Isabelle ROSA[28], Jérôme GOURNAY[29], Eric SAILLARD[30], Eric BILLAUD[31], Ventzislava PETROV-SANCHEZ[32], Alpha DIALLO[33], Hélène FONTAINE[1], Fabrice CARRAT[3,34], on behalf of the ANRS/AFEF HEPATHER study group.

1 Université Paris Descartes ; APHP, Unité d'Hépatologie, Hôpital Cochin ; INSERM U-1213 et USM20, Institut Pasteur, Paris, France

2 Department of Hepatology and Gastroenterology, Hôpital Saint Joseph, Marseille, France

3 Sorbonne Universités, UPMC Univ Paris 06, INSERM, Institut Pierre Louis d'épidémiologie et de Santé Publique (IPLESP UMRS 1136), F75012, Paris, France

4 Department of Hepatology and Gastroenterology, Hôpital Henri Mondor, AP-HP, Université Paris-Est, INSERM U955, Créteil, France

5 Liver unit-IRB-INSERM1040, Hôpital Saint Eloi, Montpellier, France

6 Department of Hepatology and Gastroenterology, Centre Hospitalier Universitaire de Nancy, Université de Lorraine, INSERM U954, Vandoeuvre-les-Nancy, France

7 Department of Hepatology and Gastroenterology, Hôpital Haut-Lévêque, Pessac, INSERM U1053, Université Bordeaux Segalen, Bordeaux, France

8 Department of Hepatology, Hospices Civils de Lyon, INSERM U1052, Université de Lyon, Lyon, France

9 Digestive Centre, Centre Hospitalier Universitaire de Nice, INSERM U1065-8, Nice, France

10 Department of Hepatology and Gastroenterology, CHU Purpan, Toulouse, France

11 Department of Hepatology and Gastroenterology, Centre Hospitalo-Universitaire, INSERM U823, Grenoble, France

12 Centre Hépato-Biliaire, Hôpital Paul Brousse, AP-HP, UMR-S785, Université Paris-Sud, INSERM U785, Villejuif, France

13 Liver disease unit, CHU Rennes, Université de Rennes 1, INSERM U991, Rennes, France

14 Department of Hepatology, Hôpital Beaujon, AP-HP, Université Paris-Diderot, INSERM CRB3, Clichy, France

15 Department of Hepatology and Gastroenterology, Dijon University Hospital, Burgundy University, INSERM U866, France.

16 Internal Medicine-Digestive Department CHU Purpan, UMR152, IRD, Toulouse 3 University, France

17 Department of Hepatology and Gastroenterology, Groupe Hospitalier Pitié-Salpétrière, AP-HP, Université Pierre et Marie Curie Paris 6, INSERM UMR-S938, Paris, France

18 Department of Hepatology, Hôpital Saint-Antoine, AP-HP,Université Pierre et Marie Curie Paris 6, Paris, France

19 Department of Hepatology and Gastroenterology, CHU Charles Nicolle, Rouen, France

20 Department of Hepatology and Gastroenterology, Hôpital Jean Verdier, AP-HP, Université Paris 13, Bondy, France

21 Department of Hepatology and Gastroenterology, Centre Hospitalier Régional et Universitaire Claude Huriez, Lille, France

22 Department of Hepatology and Gastroenterology, CHU Limoges, U850 INSERM, Univ. Limoges, F-87000 Limoges, France.

23 Unit of Hepatology, Hépatogastroenterologie, CHU Trousseau, 37044 Tours, France

24 Liver-Gastroenterology Department, CHU Angers, France

25 Inserm CIC-1434, Inserm 1110 et Pôle Hépato-digestif des Hôpitaux Universitaires de Strasbourg, Strasbourg, France.

26 Department of Hepatology and Gastroenterology, CHR La Source, Orléans, France

27 Department of Hepatology and Gastroenterology, Centre Hospitalier Régional, Metz, France

28 Department of Hepatology and Gastroenterology, Centre Hospitalier Intercommunal, Créteil, France

29 Department of Hepatology and Gastroenterology, Hôpital Hôtel-Dieu, Nantes, France

30 Department of Gastroenterology, CHU de Pointe-à-Pitre, Guadeloupe

31 Division of Infectious Diseases, University Hospital of Nantes, Nantes, France

32 ANRS (France REcherche Nord&sud Sida-vih Hépatites), Unit for Basic and Clinical research on viral hepatitis, Paris, France

33 ANRS (France REcherche Nord&sud Sida-vih Hépatites), Clinical trial safety and Public Health, Paris, France

34 Assistance Publique-Hôpitaux de Paris, Hôpital Saint Antoine, Unité de Santé Publique, F-75012 Paris, France

Correspondence :

Pr. Stanislas Pol, MD, PhD

Unité d'Hépatologie

Hôpital Cochin

27 rue du faubourg Saint Jacques

75679 Paris Cedex 14

Phone : +33 1 58 41 30 01

Fax : +33 1 58 41 30 15

Mail : stanislas.pol@aphp.fr

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Abbreviations:

-DAA: direct acting antivirals

-ANRS: National Agency for Research in HIV and Viral Hepatitis

-SVR: sustained virological response

-HCV: hepatitis C virus

-EOT: end of therapy

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Dr Carrat had full access to all the data in the study and Dr Pol and Dr Carrat had final responsibility for the decision to submit for publication

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Study concept and design: Pol, Fontaine, Carrat.

Acquisition of data: Pol, Bourlière, Hezode, Larrey, Bronowicki, De Ledinghen, Zoulim, Tran, Metivier, Zarski, Samuel, Guyader, Marcellin, Minello, Alric, Thabut, Chazouillères, Riachi, Bourcier, Mathurin, Loustaud-Ratti, D'Alteroche, Hubert, Habersetzer, Causse, Geist, Rosa, Gournay, Saillard, Billaud, Fontaine.

Analysis and interpretation of data: Pol, Lucier, Dorival, Petrov-Sanchez, Diallo, Fontaine, Carrat.

Drafting of the manuscript: Pol, Fontaine, Carrat.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Lucier, Carrat.

Obtained funding: Pol, Dorival, Petrov-Sanchez, Fontaine, Carrat.

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Study supervision: Pol, Petrov-Sanchez, Carrat.

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Abstract

Background and aims We report the first real-life results of the sofosbuvir+daclatasvir combination in HCV genotype 1 infected patients.

Methods The ANRS CO22 HEPATHER « Therapeutic options for hepatitis B and C: a French cohort » is a multicentre observational cohort which aims to include 15 000 HCV- and 10 000 HBV-infected patients. We selected all participants (n=768) with a HCV genotype 1 who initiated sofosbuvir (400 mg/d) and daclatasvir (60 mg/d) before October 1st, 2014, with or without ribavirin (1-1.2 g/d) for a duration of 12 weeks or 24 weeks. The main endpoint criteria was sustained virological response (SVR12) defined by the undetectability of HCV RNA 12 weeks after the last treatment intake. Missing SVR12 measurements were imputed using SVR24 measurements (n=45), otherwise considered as virological failure (n=18).

Results A SVR12 was obtained in 729/768 (95%) patients, ranging from 92% (12-week sofosbuvir+daclatasvir) to 99% (24-week sofosbuvir+daclatasvir+ribavirin). The SVR12 rates did not significantly differ between the 24-week (550/574 (96%)) and the 12-week (179/194 (92%); P=0.0688)) durations or between regimens with (165/169 (98%)) or without ribavirin (564/599 (94%); P=0.0850). The SVR12 rate was greater than 97% in non-cirrhotic patients irrespective of the treatment duration or the addition of ribavirin. Among cirrhotic patients, the SVR12 rate was higher with 24 than 12-week regimen (423/444 (95%) versus 105/119 (88%); P=0.0089).

Conclusion The sofosbuvir+daclatasvir combination is associated with a high rate of SVR12 in patients infected by genotype 1, with an optimal duration of 12 weeks in non-cirrhotic and 24 weeks in cirrhotic patients. The number of patients receiving ribavirin was too low to adequately assess its impact.

265 words

Lay summary

The sofosbuvir+daclatasvir combination is associated with a high rate (95 %) of viral eradication in patients infected by genotype 1,

The best duration of a ribavirin-free sofosbuvir+daclatasvir combination seems to be 12 weeks in non-cirrhotic patients and 24 weeks for those with cirrhosis.

Introduction

The very rapidly evolving field of Hepatitis C virus (HCV) therapy evidences the need for an extensive screening of HCV–infected patients and their access to antiviral treatment of patients because the high rate of sustained virological response (SVR). Antiviral therapy may be considered in any patient with chronic HCV infection as recently recommended by the European Association for the Study of the Liver (EASL).

Since 2011, the treatment of chronic hepatitis C has dramatically improved with the development of direct acting antiviral agents.

A better understanding of the viral cycle, and the characterization of viral enzymes which are potential targets, resulted in the development of new molecules, direct acting antivirals (DAA) against HCV, either specific of genotype 1 (NS3/NS4A protease inhibitors) or with a wider spectrum (NS5A and NS5B polymerase inhibitors or entry inhibitors), and non-specific antivirals [1-5]. The available drugs are in 2016 second wave of NS5B polymerase inhibitors (sofosbuvir, dasabuvir), protease inhibitor (simeprevir, paritaprevir, grazoprevir) and NS5A replication complex inhibitors (daclatasvir, then ledipasvir, ombitasvir and elbasvir) [6-7]. They have been approved, evaluated [8-24] and their combination is now recommended for treating HCV chronic infection [17-18]. Given the timelines of approvals and beyond the results of the clinical trials, real-life results of the sofosbuvir+ribavirin [25] or sofosbuvir+simeprevir combination have been extensively reported [26-28] but there are few data regarding the sofosbuvir+daclatasvir combination in genotype1-infected patients.

We report the first real-life results of the French ANRS CO22 Hepather cohort for the sofosbuvir+daclatasvir combination in genotype 1-infected patients.

Patients and methods

Study design and participants

ANRS CO22 HEPATHER cohort « Therapeutic options for hepatitis B and C: a French cohort » is a national multicentre prospective observational cohort study of patients with viral hepatitis B or C (this study is registered with ClinicalTrials.gov, number NCT01953458). The cohort was set-up in August 2012 with the main objectives to quantify the clinical efficacy and safety of new hepatitis treatments in real-life, and to identify, at the patient level, which will most likely improve overall health. The anticipated sample size was 15,000 patients with present or past chronic hepatitis C and 10,000 patients with active or inactive chronic hepatitis B, to be followed for a median duration of 7 years – this sample size would achieve a power of 80% to identify factors associated with relative risks of 3 even for rare exposures (<10%) and a low rate of event (1/1000/year). Written informed consent was obtained from each patient before enrolment. The protocol was conducted in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the "CPP Ile de France 3" Ethics Committee (Paris, France) and the French Regulatory Authority (ANSM).

HCV-positive patients were defined as patients with positive HCV-RNA or positive anti-HCV antibodies. We aimed to include at least 90% patients with chronic Hepatitis C at entry (positive HCV-RNA and anti-HCV antibodies). Main exclusion criteria for HCV-positive patients were HIV-coinfection and being on HCV-treatment at inclusion. Enrolment of patients started on August 6, 2012 in two centres and was progressively extended to 32 centres by September 2014. Participants were recruited consecutively during a medical visit at the centre. Each centre had a target number of patients to be enrolled per day adapted to its capacity. During the inclusion visit, detailed demographics, clinical (including fibrosis staging and history of past treatments) and biological data were collected using a dedicated electronic

case-report form. Blood and urines samples were collected and stored in a centralized biobank (Cell&Co Biorepository, Pont du Chateau, France). Follow-up combined systematic follow-up visits (1/year) and spontaneous reports on dedicated forms for particular events (e.g. deaths, hepatocellular carcinoma, start of therapy). In April 2014, specific instructions were given to the centres to prioritize the inclusion of patients with chronic hepatitis C who will start a treatment against HCV. The follow-up was modified accordingly to include local HCV-RNA evaluations at initiation of treatment (Day 0-D0), week 1 (W1), W2, W4, W12, W24, End of Therapy (EOT) and 4, 12 and 24 weeks after the last treatment intake. HCV-RNA measurements were performed locally and varied across centres according to the assay (Roche or Abbott mainly in France) and the threshold of detection (12 or 15 IU/mL). All adverse events were reported irrespective of their potential relationship with antiviral drugs. Additionally, any dose modification or treatment discontinuation was reported. The study was observational and the choice of the treatment combination was left to physician discretion.

By Sept 8, 2015, 13,832 HCV-positive patients had been included in the cohort of which 4836 patients were given a treatment including at least one direct acting antiviral and of these 4459 received an interferon-free regimen. We selected all patients with HCV Genotype 1 infection who initiated a combination of sofosbuvir (400 mg/d) and daclatasvir (60 mg/d) with or without ribavirin (1-1.2 g/d) before Oct 1, 2014 to ensure sufficient follow-up information (n=768). We excluded patients who were: liver transplant recipients, included in a clinical trial, or received other DAAs therapy (except first generation protease inhibitors) before initiation of the sofosbuvir+daclatasvir combination. Diagnosis of cirrhosis was based either on the results of a liver biopsy, a liver stiffness value $\geq$ 12.5 kPa by Fibroscan® and/or a Fibrotest® result $\geq$ 0.73. Four groups of patients were defined according to the anticipated duration of treatment and whether the regimen contained ribavirin. Treatment duration and addition of ribavirin was according to the discretion of the treating physician.

Outcomes

The main endpoint criterion was SVR at 12 weeks (SVR12) defined by the undetectability of HCV RNA 12 weeks after the last treatment intake. Secondary endpoints were undetectability of HCV RNA 4 weeks after last treatment intake (SVR4), premature treatment discontinuation and adverse events.

Statistical analyses

The present study achieved a precision of 2% around an anticipated 90% SVR12 and had a power > 80% for detecting Odds-Ratio (OR) < 0.4 for factors associated with SVR12 assuming exposure to these factors ranged between 30 to 70%. Missing SVR12 measurements were imputed using SVR24 measurement if available (n=45), otherwise were imputed as a virological failure in 18 patients (5 patients who died before the SVR12 visit; 3 patients who were responders at 12 weeks on treatment but were lost to follow-up thereafter; 10 patients with SVR4 measurements among whom 3 were responders 4 weeks after last treatment intake, 7 were not responders). Proportions were compared using the Fisher exact test or and continuous outcomes were compared using the Mann-Whitney test. Cochran-Mantel Haenszel (CMH) Chi-Square was used for comparisons with stratification on treatment duration or on ribavirin-containing regimen. To identify independent baseline variables associated with SVR12 or associated with serious adverse events (including deaths), we used exact logistic regression models. All continuous factors were categorized using predefined thresholds. For each factor, a univariate exact logistic model was estimated. The primary multivariate analysis included ribavirin (No vs Yes), treatment duration (12 vs. 24 weeks) and all factors with a P-value <0.10 in univariate analysis. A backward selection was applied retaining variables with a P-value <0.05. This analytic framework was repeated in the subset of

cirrhotic patients. In addition, to control for potential indication bias in the analysis of SVR12 predictors, we performed sensitivity analyses, taking into account the propensity of being treated with ribavirin or for 24 weeks (vs 12 weeks). The propensity scores were computed using covariates values at start of treatment using logistic regression models. The predicted probabilities of being treated with ribavirin or for 24 weeks were discretized in quintiles and used as a stratification factor in a multivariate conditional exact logistic regression model. All analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

Role of the funding source

INSERM-ANRS had a role in study design, data collection, data analysis, data interpretation, and approval of the final report. The funders of the study other than INSERM-ANRS had no role in study design, data collection, data analysis, data interpretation, or writing of the report. FC had full access to all the data in the study and SP and FC had final responsibility for the decision to submit for publication.

Results

By Oct 1, 2014, 768 cohort participants with a HCV genotype 1 infection had started a sofosbuvir+daclatasvir combination of which 599 (78%) did not receive and 169 (22%) did receive ribavirin according to the physician (figure 1). One hundred and ninety-four (25%) patients were treated for 12 weeks, and 574 (75%) were treated for 24 weeks, with no difference according to whether the regimen contained ribavirin (P=0.0886). The patient characteristics are described in table 1. Patients who received a 12-week combination of sofosbuvir+daclatasvir had a lower rate of cirrhosis and were more frequently treatment naïve than patients who received a 24-week or a ribavirin-containing regimen.

A SVR12 was obtained in 729 (95%) patients. Among the 39 patients who did not obtain a SVR12: 32 (82%) were treated for more than 8 weeks. Of these, 4 never had undetectable HCV-RNA during therapy, 6 had undetectable HCV-RNA but experienced a breakthrough during therapy and 22 had undetectable HCV-RNA at the end of therapy and experienced a relapse during the follow-up. The remaining 7 (22%) patients with SVR12 failure and less than 8 weeks of therapy did not achieve any undetectable HCV-RNA during therapy. The SVR12 rates ranged between 92% in patients who received a 12-week sofosbuvir+daclatasvir combination regimen to 99% in patients who received a 24-week sofosbuvir+daclatasvir+ribavirin combination regimen (table 2). No significant difference in SVR12 rates was noticed either between the 24-week duration compared with the 12-week duration (550/574 (96%) versus 179/194 (92%), (CMH Chi Square stratified on ribavirin containing regimen: P=0.0688) or between the sofosbuvir+daclatasvir and sofosbuvir+daclatasvir+ribavirin regimens (564/599 (94%) versus 165/169 (98%))(CMH Chi Square stratified on treatment duration: P=0.0850). The SVR12 rate was greater than 97% in non-cirrhotic patients irrespective of the treatment group. Among cirrhotic patients, the SVR12 rate was higher in those who received a 24-week regimen than in those who received

a 12-week regimen (423/444 (95%) versus 105/119 (88%)(CMH Chi Square stratified on ribavirin containing regimen: P=0.0054). There was no difference in SVR12 between HCV genotype 1a and 1b subtypes (CMH stratified on treatment duration and ribavirin-containing regimen: P=0.5497) .

Univariate analysis identified treatment history, cirrhosis and albumin as variables to consider for further multivariate analysis of factors associated with SVR12 (table 3). Absence of cirrhosis (vs cirrhosis), being treatment-experienced (vs treatment-naïve) and albumin ≥ 30 g/L (vs albumin <30 g/L) remained independent predictors of SVR12.

When the analysis was repeated in the subset of cirrhotic patients, we found an association of SVR12 with treatment duration (univariate odds-ratio (OR) for 24 weeks versus 12 weeks 2.68 (95%CI 1.22 – 5.74; P=0.0138)) and with past treatment history (OR for treatment-naïve versus treatment-experienced patients 0.24 (95%CI 0.11 – 0.54; P=0.0005)), while no association with ribavirin (OR for ribavirin containing versus not containing regimen, 2.35 (95%CI 0.81 – 9.35; P=0.1433)). The association with treatment duration did not remain significant once adjusted on other variables (multivariate adjusted OR for 24 weeks versus 12 weeks treatment duration 1.86 (95%CI 0.79 – 4.24; P=0.1671)).

When the analysis was stratified on the propensity to receive ribavirin or on the propensity to receive a 24-week regimen, SVR12 was no longer associated with past treatment history, while associations with cirrhosis and albumin remained globally unchanged (see supplementary material).

Premature treatment discontinuation occurred in 54 (7%) patients, and was more frequent in patients receiving a ribavirin containing regimen (CMH Chi Square stratified on treatment duration: P<0.0001) (table 4). Among patients who discontinued treatment, 43 (80%) achieved a SVR12 and 40 (93%) had been treated for more than 8 weeks; 11 (20%) did not achieve a SVR12 and 4 (36%) had been treated for more than 8 weeks, respectively. Five

patients died during the follow-up: one patient died 6 weeks after treatment initiation from cerebral hemorrhage and death was considered as possibly related to the treatment (sofosbuvir+daclatasvir) ; two patients died from end stage liver disease (hepatic cirrhosis at week 11, hepatic encephalopathy at week 24) and two patients died from septic shock at 25 and 29 weeks: these 4 deaths were not considered treatment-related. Other serious adverse events occurred in 78 (10%) patients irrespective of treatment duration or ribavirin containing regimen. Six of these serious adverse events were considered as being possibly related to the treatment: 3 were cardiac disorders (one atrial flutter at day 4 related to sofosbuvir+daclatasvir; one bradycardia at day 1 related to sofosbuvir and one cardiac failure at day 20 after treatment initiation related to ribavirin). The most common adverse events (in ≥10% of patients) were asthenia, headache, and insomnia. Univariate analysis identified treatment duration, decompensated cirrhosis, prothrombin time < 70% and serum albumin <30g/L as potential predictors of serious adverse events. The only two factors independently associated with serious adverse events were decompensated cirrhosis (OR versus no decompensated cirrhosis, 3.48 95%CI 1.56-7.51; P=0.0021) and prothrombin time < 70% (OR versus prothrombin time < 70%, 2.20 95%CI 1.17-4.02; P=0.0135). Of note, age, gender, time since HCV diagnosis, cirrhosis were not associated with serious adverse events.

Discussion

This is the first report of the real life results of the sofosbuvir+daclatasvir combination in genotype 1-infected patients. We showed that the sofosbuvir+daclatasvir combination was associated with a high SVR12 rate and we explored the impact of treatment duration and ribavirin combination in patients infected with HCV genotype 1. Cirrhosis was strongly associated with treatment failure. Almost all non-cirrhotic patients achieved a SVR irrespective of the treatment schedule and a 12-week course of the sofosbuvir+daclatasvir combination without ribavirin appears to be the primary therapeutic choice. On the contrary, cirrhotic patients need optimised therapy, and a higher rate of SVR was obtained with a 24-week course of the sofosbuvir+daclatasvir combination. Notably, when focusing on predictors of SVR12 in cirrhotic patients, a 24-week regimen did not appear to be significantly better than a 12-week regimen after multivariate adjustment on previous treatment history and ribavirin-containing regimen; this may be due to the low number of SVR12 failure and lack of power. Similarly, there was no significant increase in SVR12 in cirrhotic patients receiving a 12-week combination of sofosbuvir+daclatasvir+ribavirin, but few patients were included in this subgroup and our analysis was clearly underpowered to draw relevant conclusions on this subgroup. Our findings were consistent with the double-blind controlled Sirius trial conducted in French cirrhotic patients who failed to respond to prior Peginterferon+ribavirin (PR) and PR + first generation protease inhibitor therapy [29]: in this trial, the rate of adverse events was similar in the placebo arm (82%) and in the ledipasvir (another NS5A inhibitor)+sofosbuvir arm without (85%) or with (87%) ribavirin during the first 12 weeks of analysis [29]; patient-reported outcomes improved in both treated arms with or without ribavirin as compared to the placebo arm during and after the treatment, even if ribavirin negatively impacted patient-reported outcomes [30].

Strikingly, we identified a lower SVR12 rate in treatment-naïve patients versus treatment-experienced patients. Detailed examination showed that 184 of 186 (99%) treatment-experienced patients who were former responders (with a relapse or a breakthrough) at previous HCV therapy achieved a SVR12 with sofosbuvir+daclatasvir (P<0.0001 compared to 88% SVR12 in 111/126 treatment naïve patients) which might partly explain this finding. However patients who were not responders to the last HCV therapy also achieved a higher SVR12 rate compared to treatment naïve patients (412/432 (95%) versus 111/126 (88%), P= 0.0057). This difference may be due to different selection profiles and history of care or compliance between treatment-experienced and treatment-naïve patients.

The virological analysis of failures is in progress but is not yet available even if some of these failures have been recently reported [31]. Most virological failures were relapses rather than virological breakthroughs, and we can expect as previously observed that treatment failures will be mainly associated with resistance-associated variants.

Our study has several limitations. First, due to the observational nature no definite conclusion can be drawn on the superiority of a regimen compared to another and despite our efforts to control for confounding and numerous sensitivity analyses, residual confounding may be present. Second, the number of patients in the 12-week regimen with ribavirin was low as was the total number of observed virological failures, which limits the power of our study and may have altered the robustness of some findings.

In conclusion, in real life, the sofosbuvir+daclatasvir combination in difficult-to-treat patients with HCV Genotype 1 infection was associated with a high rate of SVR12. Cirrhosis was strongly linked to treatment failure. A ribavirin-free sofosbuvir+daclatasvir regimen given for 12 weeks in patients without cirrhosis, and for 24 weeks in those with cirrhosis was associated with highest SVR rates. The number of patients with cirrhosis receiving ribavirin was too

small to judge whether a 12 week ribavirin-containing sofosbuvir+daclatasvir regimen might be competitive as compared to the 24 week ribavirin-free regimen for this population.

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Figure legends :

Figure 1: flow diagram

ANRS-AFEF Hepather Study group

Delphine Bonnet, Virginie Sicart (CHU Purpan, Toulouse, France), François Bailly, Marjolaine Beaudoin, Dominique Giboz, Kerstin Hartig-Lavie, Marianne Maynard (Hospices Civils de Lyon, Lyon, France), Morane Cavellec, Marjorie Cheraud-Carpentier, François Raffi, Florian Vivrel (Hôpital Hôtel-Dieu, Nantes, France), Jaouad Benhida, Jérôme Boursier, Paul Calès, Françoise Lunel, Frédéric Oberti (CHU Angers, Angers, France), Nathalie Boyer, Audrey Gilibert, Nathalie Giuily (Hôpital Beaujon, Clichy, France), Giovanna Scoazec (Hôpital Beaujon, Clichy, France and Hôpital Henri Mondor, Créteil, France), Sandrine Fernandes, Sylvie Keser, Philippe Sultanik, Anaïs Vallet-Pichard (Hôpital Cochin, Paris, France), Juliette Foucher, Jean-Baptiste Hiriart, Aurore Mathias, Julien Vergniol (Hôpital Haut-Lévêque, Pessac, Bordeaux, France), Chrystelle Ansaldi, Laëtitia Chouquet, Emilie De Luca, Valérie Oules (Hôpital Saint Joseph, Marseille, France), Rodolphe Anty, Eve Gelsi, Régine Truchi (CHU de Nice, Nice, France), Elena Luckina, Nadia Messaoudi, Joseph Moussali, (Groupe Hospitalier Pitié-Salpétrière, Paris, France), Barbara De Dieuleveult, Damien Labarriere, Pascal Poter, Si Nafa Si Ahmed (CHR La Source, Orléans, France), Nathalie Ganne-Carrié, Véronique Grando-Lemaire, Pierre Nahon, Alan Peltier, Judith Ung (Hôpital Jean Verdier, Bondy, France), Mariette Gougeon, Anne Guillygomarch, Caroline Jezequel (CHU Rennes, Rennes, France), Romain Moirand, Thomas F. Baumert, Michel Dofföel, Catherine Mutter, Pauline Simo-Noumbissie (Hôpitaux Universitaires de Strasbourg, Strasbourg, France), Hélène Barraud, Mouni Bensenane, Abdelbasset Nani, Sarah Hassani-Nani (CHU de Nancy, Vandoeuvre-lès-Nancy, France), Marie-Albertine Bernard (CHU de Nancy, Vandoeuvre-lès-Nancy, France and Centre Hospitalier Régional, Metz, France), Michael Bismuth, Ludovic Caillo, Stéphanie Faure, Georges-Philippe Pageaux, Marie Pierre Ripault (Hôpital Saint Eloi, Montpellier, France), Karl Barange, Christophe Bureau, Jean Marie Peron, Marie Angèle Robic, Léa Tarallo (CHU Purpan, Toulouse, France), Marine Faure, Bruno Froissart, Marie-Noelle Hilleret, Vincent Leroy (CHU de Grenoble, Grenoble, France), Odile Goria, Victorien Grard, Hélène Montialoux (CHU Charles Nicolle, Rouen,

France), Muriel François, Christian Ouedraogo, Christelle Pauleau, Anne Varault (Hôpital Henri Mondor, Créteil, France), Tony Andreani, Bénédicte Angoulevant, Azeline Chevance, Lawrence Serfaty (Hôpital Saint-Antoine, Paris, France), Teresa Antonini, Audrey Coilly, Jean-Charles Duclos Vallée, Mariagrazia Tateo (Hôpital Paul Brousse, Villejuif, France), Armand Abergel, Corinne Bonny, Chanteranne Brigitte, Géraldine Lamblin, Léon Muti (Hôpital Estaing, Clermont-Ferrand, France), Abdenour Babouri, Virginie Filipe (Centre Hospitalier Régional, Metz, France), Camille Barrault, Laurent Costes, Hervé Hagège, Soraya Merbah (Centre Hospitalier Intercommunal, Créteil, France), Paul Carrier, Maryline Debette-Gratien, Jérémie Jacques (CHU Limoges, Limoges, France), Florent Artu, Valérie Canva, Sébastien Dharancy, Alexandre Louvet (CHRU Claude Huriez, Lille, France), Marc Bardou, Donya Da Costa Souhiel, Patrick Hillon, Marianne Latournerie (Dijon University Hospital, Dijon, France), Yannick Bacq, Didier Barbereau, Charlotte Nicolas (CHU Trousseau, 37044 Tours, France), Nisserine Ben Amara, Danièle Botta-Fridlund, Isabelle Portal (CHU Timone, Marseille, France), Moana Gelu-Simeon, Marie-Josée Lafrance (CHU de Pointe-à-Pitre, Pointe-à-Pitre, Guadeloupe).

Scientific Committee:

- Voting members :

Marc Bourlière (Hôpital St Joseph, Marseille, Paris), Patrice Cacoub (Hôpital Pitié salpêtrière, Paris, France), Jacqueline Capeau (lnserm U680 Faculté de médecine Saint Antoine, Paris, France), Fabrice Carrat (Scientific Coordinator, Hôpital Saint-Antoine, Paris, France), Patrizia Carrieri (INSERM U912, Marseille, France), Victor De Ledinghen (Hôpital Haut-Lévêque, Pessac, Bordeaux, France), Céline Dorival (UPMC & INSERM U1136, Paris, France), Jean Dubuisson (Inserm U1019, Lille, France), Hélène Fontaine (Hôpital Cochin, Paris, France), Dominique Larrey (Hôpital Saint Eloi, Montpellier, France), Christine Larsen (Institut de veille Sanitaire, Saint-Maurice, France), Patrick Marcellin (Hôpital Beaujon, Clichy, France), Philippe Mathurin (CHRU Claude Huriez, Lille, France), Pierre Nahon (Hôpital Jean Verdier, Bondy, France), Francesco Negro (Hôpital Cantonal Universitaire, Genève, Suisse), Georges-Philippe Pageaux (Hôpital Saint Eloi, Montpellier, France), Jean-Michel Pawlotsky (Hôpital Henri Mondor, Créteil, France), Ventzislava Petrov-Sanchez (ANRS, Paris, France), Stanislas Pol (Principal Investigator, Hôpital Cochin, Paris, France), Linda Wittkop (ISPED-INSERM U897,

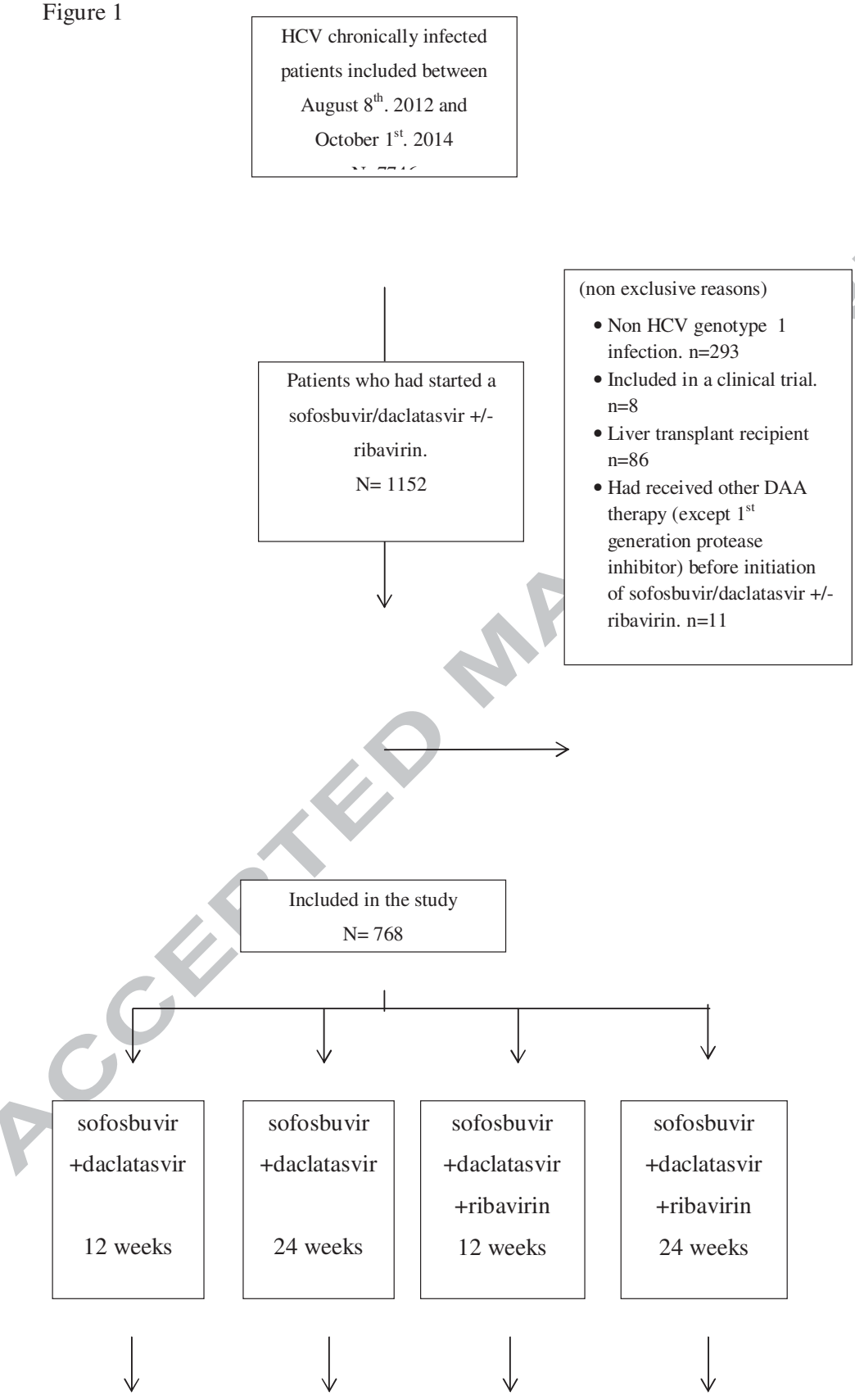
Bordeaux, France), Yazdan Yazdanpanah (Hôpital Bichat Claude Bernard, Paris, France), Jean-Pierre Zarski (CHU de Grenoble, Grenoble, France), Fabien Zoulim (Hospices Civils de Lyon, Lyon, France).

- Non voting members:
Marianne L'hennaff (ARCAT-TRT-5-CHV, France), Michèle Sizorin (SOS hépatites, France); one representative of INSERM-ANRS Pharmacovigilance team, Paris, France (Imane Amri, Alpha Diallo), Mélanie Simony (INSERM-ANRS, Paris, France), one member of Inserm Transfert, Paris, France (Françoise Crevel, Mireille Caralp), and one representative of each pharmaceutical company (MSD, Janssen, Gilead, Abbvie, BMS, Roche).

Sponsor: Imane Amri, Alpha Diallo, Ventzi Petrov-Sanchez (coordinator), Mélanie Simony and Carole Cagnot (INSERM-ANRS, Paris, France).

Methodology and Coordinating Centre: Lynsée Anastase, Manon Bergier, Vincent Bonnemains, Fabrice Carrat (coordinator), Frederic Chau, Céline Dorival, Sarita Ghanem, Isabelle Goderel, Georges Haour, Sandy Lucier, Ophélie Lutton, Godwin Mawuvi, Caroline Montaudouin, Dorian Multedo, Elodie Munier, Marion Pirot, Noëlle Pouget, Evelyne Rasamoelina, Claire Vezier (UPMC & INSERM U1136, Paris, France).

Figure 1



Analyzed N=160	Analyzed N=439	Analyzed N=34	Analyzed N=135

Table 1· Baseline characteristics of patients according to treatment regimen·

	Sofosbuvir+daclatasvir		Sofosbuvir+daclatasvir +ribavirin		P-Value
	12 weeks n=160	24 weeks n=439	12 weeks n=34	24 weeks n=135	
Age (Years). Mean ± SD	61 ± 11	60 ± 10	60 ± 11	57 ± 9	0·0568
Gender Male	100 (63)	273 (62)	26 (76)	91 (67)	0·2843
BMI (Kg/m2)					
<18·5	5 (3)	7 (2)	1 (3)	3 (2)	
[18·5-25[	86 (54)	202 (46)	11 (32)	74 (55)	0·2636
[25-30[	47 (29)	158 (36)	16 (47)	40 (30)	
≥30	22 (14)	70 (16)	6 (18)	18 (13)	
Chronic hepatitis duration (Years). Mean ± SD	15 ± 8	15 ± 7	14 ±7	15 ± 7	0·7043
HCV genotype					
1a	73 (46)	210 (48)	14 (41)	84 (62)	0·0224
1b	83 (52)	209 (48)	18 (53)	45 (33)	
1 not subtyped	4 (3)	20 (5)	2 (6)	6 (4)	
Diabetes	20 (13)	98 (22)	4 (12)	22 (16)	0·0243
Hypertension	53 (33)	151 (34)	12 (35)	40 (30)	0·7489
MELD Score. Mean ± SD [a]	8·2 ± 3·2	8·5 ± 4·0	7·4 ± 2·4	9·2 ± 4·3	0·0484
MELD score<13[a]	136 (91)	356 (86)	27 (96)	100 (85)	0·1936
Cirrhosis	94 (59)	342 (78)	25 (74)	102 (76)	<0·0001
Child-Pugh score B or C	11 (20)	38 (17)	2 (29)	11 (18)	0.7227
MELD Score. Mean± SD	8.9±3.6	8.7±4.1	7.6±2.6	9.5±4.5	0.0692
Liver biopsy < 2yrs	2 (2)	19 (6)	4 (16)	8 (8)	0.0497
Liver biopsy ≥ 2 yrs	46 (49)	214 (63)	14 (56)	61 (60)	0.1196
Elastography (≥ 12.5 kPa)	55 (59)	237 (69)	14 (56)	58 (57)	0.0370
Fibrotest® (≥ 0.73)	5 (5)	23 (7)	1 (4)	13 (13)	0.1752
Decompensated cirrhosis	9 (6)	30 (7)	0 (0)	9 (7)	0·4987
Child-Pugh score B or C	5 (71)	13 (57)	0 (0)	7 (78)	0.0573
MELD Score. Mean± SD	12.8±4.3	11.5±3.2	-	13.4±5.1	0.5528
Albumin (<30g/L)[b]	11 (7)	39 (10)	0 (0)	8 (7)	0·2223
Prothrombin time (<70%)[c]	24 (16)	59 (14)	3 (10)	26 (21)	0·2256
AST (>5 x ULN)[d]	7 (4)	57 (13)	1 (3)	21 (16)	0·0015
ALT (>5 x ULN)[e]	14 (9)	58 (14)	0 (0)	18 (14)	0·0397
Haemoglobin (<12g/dL in women or <13g/dL in men)[f]	27 (17)	81 (19)	4 (12)	18 (14)	0.5404
Treatment history	64 (40)	48 (11)	3 (9)	11 (8)	<0·0001

naïve patients	68 (43)	172 (39)	9 (26)	64 (47)	
experienced patients. last treatment PEG/RIB	28 (18)	219 (50)	22 (65)	60 (44)	
experienced patients. last treatment 1st G PI/PEG/RIB					
Response profile in treatment experienced patients					0·1408
Not responders	65 (41)	256 (58)	17 (50)	94 (70)	
Responders[g]	29 (18)	119 (27)	11 (32)	27 (19)	
Unknown	2 (1)	16 (4)	3 (9)	3 (3)	

Numbers are N (%) otherwise specified. [a] missing in 61. [b] missing in 69. [c] missing in 61. [d] missing in 20. [e] missing in 16. [f] missing in 19. [g] responders = patients with negative HCV RNA on last treatment – includes 1 patient with sustained virological response who was re-infected.

Table2: Virological responses according to treatment regimen

	Sofosbuvir + daclatasvir		Sofosbuvir + daclatasvir + ribavirin		P-value
	12 weeks n=160	24 weeks n=439	12 weeks n=34	24 weeks n=135	
Negative HCV RNA					
Week 2	31/140 (22)	65/400 (16)	6/31 (19)	12/114 (11)	0.0874
Week 4	71/145 (49)	207/426 (49)	18/34 (53)	37/131 (28)	0.0002
Week 12	135/154 (88)	384/431 (89)	31/32 (97)	109/134 (81)	0.0456
Week 24		418/428 (98)		130/132 (98)	0.7408
SVR4	128/133 (96)	363/376 (97)	24/26 (92)	118/118 (100)	0.0472
SVR12[a]	147/160 (92)	417/439 (95)	32/34 (94)	133/135 (99)	0.0561
SVR24	137/141 (97)	335/344 (97)	28/28 (100)	109/109 (100)	0.3386
SVR12 in non cirrhotic patients	65/66 (98)	94/97 (97)	9/9 (100)	33/33 (100)	0.7183
SVR12 in cirrhotic patients	82/94 (87)	323/342 (94)	23/25 (92)	100/102 (98)	0.0152
SVR12 in treatment naïve patients	56/64 (88)	41/48 (85)	3/3 (100)	11/11 (100)	0.7285
SVR12 in treatment experienced patients	91/96 (95)	376/391 (96)	29/31 (94)	122/124 (98)	0.3140
Last treatment					
PEG/RIB	65/68 (96)	166/172 (97)	8/9 (89)	63/64 (98)	0.3653
1st G PI/PEG/RIB	26/28 (93)	210/219 (96)	21/22 (95)	59/60 (98)	0.5393
Response profile					
Not responders	60/65 (92)	245/256 (96)	15/17 (88)	92/94 (98)	0.1352
Responders[b]	29/29 (100)	117/119 (98)	11/11 (100)	27/27 (100)	0.9999
Unknown	2/2 (100)	14/16 (88)	3/3 (100)	3/3 (100)	0.9999
SVR12 in patients with genotype 1a infection	69/73 (95)	199/210 (95)	13/14 (93)	83/84 (99)	0.2906
SVR12 in patients with genotype 1b infection	74/83 (89)	199/209 (95)	17/18 (94)	44/45 (98)	0.1694

[a] Missing SVR12 were imputed using SVR24 in 45 patients. otherwise were imputed as a virological failure in 18 patients.

[b] responders = patients with negative HCV RNA on last treatment – includes 1 patient with sustained virological response who was re-infected.

Table 3: Variables associated with SVR12.

		Univariate		Multivariate	
Variable	n with SVR 12 / Total (%)	OR (95% CI)	P-value	OR (95% CI)	P-value
Ribavirin containing regimen [a]					
No	564/599 (94)	ref		ref	
Yes	165/169 (98)	2.56 (0.9-10.05)	0.0903	2.06 (0.70-8.23)	0.2492
Treatment duration [a]					
12 weeks	179/194 (92)	ref		ref	
24 weeks	550/574 (96)	1.92 (0.91-3.91)	0.0867	1.63 (0.71-3.60)	0.2734
Treatment history					
Treatment experienced	618/642 (96)	ref		ref	
Treatment naïve	111/126 (88)	0.29 (0.14-0.61)	0.0011	0.39 (0.17-0.89)	0.0250
Cirrhosis					
No	201/205 (98)	ref		ref	
Yes	528/563 (94)	0.3 (0.08-0.86)	0.0191	0.31 (0.08-0.94)	0.0348
Albumin					
≥30g/L	613/642 (95)	ref		ref	
< 30g/L	48/57 (84)	0.25 (0.11-0.64)	0.0043	0.37 (0.15-0.99)	0.0472
missing	68/69 (99)	3.21 (0.52-133)	0.3826	2.67 (0.42-112)	0.5598

[a] Treatment duration and ribavirin containing regimen were included in the multivariate analysis irrespective of the p-value in univariate analysis. Other variables with p-value <0·1 in univariate analysis were included in a multivariate model and selected according to a backward selection

Table 4: Treatment discontinuation. adverse events and serious adverse events according to treatment regimens.

	Sofosbuvir+daclatasvir		Sofosbuvir+daclatasvir+ribavirin		**P-value**
	12 weeks	24 weeks	12 weeks	24 weeks	
Number of patients	159	437	34	135	
Treatment discontinuation	16 (10)	9 (2)	0 (0)	29 (21)	<0·0001
Intolerance or adverse event	8 (5)	5 (1)	0 (0)	24 (18)	<0·0001
Other reasons	8 (5)	4 (1)	0 (0)	5 (4)	0·0090
All adverse events -any (maximum grade)	96 (60)	338 (77)	24 (71)	114 (84)	<0·0001
grade 1	48 (30)	111 (25)	15 (44)	26 (19)	
grade 2	28 (18)	150 (34)	6 (18)	65 (48)	
grade 3	10 (6)	49 (11)	2 (6)	10 (7)	<0·0001
grade 4	8 (5)	25 (6)	1 (3)	13 (10)	
grade 5	2 (1)	3 (1)	0 (0)	0 (0)	
Deaths	2 (1)	3 (1)	0 (0)	0 (0)	0·6579
Other Serious Adverse Events	10 (6)	47 (11)	2 (6)	19 (14)	0·1332
Adverse Events (≥10% in any subgroup)					
Asthenia	33 (21)	110 (25)	9 (26)	55 (41)	0·0011
Headache	22 (14)	96 (22)	4 (12)	21 (16)	0·0651
Insomnia	8 (5)	47 (11)	2 (6)	17 (13)	0·0839
Fatigue	14 (9)	33 (8)	5 (15)	12 (9)	0·4605
Leukopenia	3 (2)	27 (6)	2 (6)	13 (10)	0·0276
Irritability	5 (3)	21 (5)	2 (6)	13 (10)	0·0866
Pruritus	1 (1)	24 (5)	5 (15)	11 (8)	0·0006
Hyperbilirubinaemia	3 (2)	18 (4)	2 (6)	15 (11)	0·0034

Sofosbuvir (400 mg/d)+ Daclatasvir (60 mg/d) in HCV genotype 1-infection

768 patients from the ANRS CO22 Hepather cohort

- SVR_{12} (ITT) = 95% (729/768) ranging from 92% (12 weeks duration) to 99% (24 weeks duration)
- No impact of Ribavirin or treatment duration in non cirrhotic patients
- Higher SVR12 rate in cirrhotics with 24 vs. 12 weeks
- Fair tolerance

HCV genotype 1-infected patients treated by Sofosbuvir+ Daclatasvir:

- 12 weeks for non cirrhotics
- 24 weeks for cirrhotics