Research Article

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Viral Hepatitis

Safety and efficacy of daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients

Stanislas Pol[1,*], Marc Bourliere[2], Sandy Lucier[3], Christophe Hezode[4], Céline Dorival[3], Dominique Larrey[5], Jean-Pierre Bronowicki[6], Victor D.E. Ledinghen[7,8], Fabien Zoulim[9], Albert Tran[10], Sophie Metivier[11], Jean-Pierre Zarski[12], Didier Samuel[13], Dominique Guyader[14], Patrick Marcellin[15], Anne Minello[16], Laurent Alric[17], Dominique Thabut[18], Olivier Chazouilleres[19], Ghassan Riachi[20], Valérie Bourcier[21], Philippe Mathurin[22], Véronique Loustaud-Ratti[23], Louis D'Alteroche[24], Isabelle Fouchard-Hubert[25], François Habersetzer[26], Xavier Causse[27], Claire Geist[28], Isabelle Rosa[29], Jérôme Gournay[30], Eric Saillard[31], Eric Billaud[32], Ventzislava Petrov-Sanchez[33], Alpha Diallo[34], Hélène Fontaine[1], Fabrice Carrat[3,35], on behalf of the ANRS/AFEF HEPATHER study group

[1]*Université Paris Descartes, AP-HP, 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-lès-nancy, France;* [7]*Department of Hepatology and Gastroenterology, Hôpital Haut-Lévêque, Pessac, France;* [8]*INSERM, U1053, Université Bordeaux Segalen, Bordeaux, France;* [9]*Department of Hepatology, Hospices Civils de Lyon, INSERM U1052, Université de Lyon, Lyon, France;* [10]*Digestive Centre, Centre Hospitalier Universitaire de Nice, INSERM U1065-8, Nice, France;* [11]*Department of Hepatology and Gastroenterology, CHU Purpan, Toulouse, France;* [12]*Department of Hepatology and Gastroenterology, Centre Hospitalo-Universitaire, INSERM U823, Grenoble, France;* [13]*Centre Hépato-Biliaire, Hôpital Paul Brousse, AP-HP, UMR-S785, Université Paris-Sud, INSERM U785, Villejuif, France;* [14]*Liver Disease Unit, CHU Rennes, Université de Rennes 1, INSERM U991, Rennes, France;* [15]*Department of Hepatology, Hôpital Beaujon, AP-HP, Université Paris-Diderot, INSERM CRB3, Clichy, France;* [16]*Department of Hepatology and Gastroenterology, Dijon University Hospital, Burgundy University, INSERM U866, France;* [17]*Internal Medicine-Digestive Department CHU Purpan, UMR152, IRD, Toulouse 3 University, France;* [18]*Department of Hepatology and Gastroenterology, Groupe Hospitalier Pitié-Salpétrière, AP-HP, Université Pierre et Marie Curie Paris 6, INSERM UMR-S938, Paris, France;* [19]*Department of Hepatology, Hôpital Saint-Antoine, AP-HP, Université Pierre et Marie Curie Paris 6, Paris, France;* [20]*Department of Hepatology and Gastroenterology, CHU Charles Nicolle, Rouen, France;* [21]*Department of Hepatology and Gastroenterology, Hôpital Jean Verdier, AP-HP, Université Paris 13, Bondy, France;* [22]*Department of Hepatology and Gastroenterology, Centre Hospitalier Régional et Universitaire Claude Huriez, Lille, France;* [23]*Department of Hepatology and Gastroenterology, CHU Limoges, U850 INSERM, Univ. Limoges, F-87000 Limoges, France;* [24]*Unit of Hepatology, Hépatogastroenterologie, CHU Trousseau, 37044 Tours, France;* [25]*Liver-Gastroenterology Department, CHU Angers, France;* [26]*Inserm CIC-1434, Inserm 1110 et Pôle Hépato-digestif des Hôpitaux Universitaires de Strasbourg, Strasbourg, France;* [27]*Department of Hepatology and Gastroenterology, CHR La Source, Orléans, France;* [28]*Department of Hepatology and Gastroenterology, Centre Hospitalier Régional, Metz, France;* [29]*Department of Hepatology and Gastroenterology, Centre Hospitalier Intercommunal, Créteil, France;* [30]*Department of Hepatology and Gastroenterology, Hôpital Hôtel-Dieu, Nantes, France;* [31]*Department of Gastroenterology, CHU de Pointe-à-Pitre, Guadeloupe, France;* [32]*Division of Infectious Diseases, University Hospital of Nantes, Nantes, France;* [33]*ANRS (France REcherche Nord&sud Sida-vih Hépatites), Unit for Basic and Clinical Research on Viral Hepatitis, Paris, France;* [34]*ANRS (France REcherche Nord&sud Sida-vih Hépatites), Clinical Trial Safety and Public Health, Paris, France;* [35]*Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Antoine, Unité de Santé Publique, F-75012 Paris, France*

Background & Aims: We report the first real-life results of the sofosbuvir + daclatasvir combination in hepatitis C virus (HCV) genotype 1 infected patients.

Methods: The France REcherche Nord&Sud Sida-hiv Hépatites (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/day) and daclatasvir (60 mg/day) before October 1st 2014, with or without ribavirin (1–1.2 g/day) for a duration of 12 weeks or 24 weeks. The main endpoint criterion was sustained virological response at 12 weeks (SVR12), defined by the absence of detectable HCV-RNA 12 weeks after the last treatment intake. Missing SVR12 measurements were imputed using SVR24

Keywords: Chronic hepatitis C; Treatment; Sofosbuvir; Daclatasvir; Direct antiviral agents; Cirrhosis; Severe fibrosis; Genotype 1; Hepather cohort.
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* Corresponding author. Address: Unité d'Hépatologie, Hôpital Cochin, 27 rue du faubourg Saint Jacques, 75679 Paris Cedex 14, France. Tel.: +33 1 58 41 30 01; fax: +33 1 58 41 30 15.
E-mail address: stanislas.pol@aphp.fr (S. Pol).

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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%) *vs.* 105/119 (88%); $p = 0.0054$).

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.

Lay summary: The sofosbuvir + daclatasvir combination of antiviral drugs is associated with a high rate (95%) of viral eradication in patients infected by HCV 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.

Clinical trial number: NCT01953458.

Introduction

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

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

A better understanding of the viral lifecycle, and the characterization of viral enzymes, which are potential targets, has resulted in the development of new molecules, DAAs against HCV. These are either specific for genotype 1 (NS3/NS4A protease inhibitors) or cover a wider spectrum (NS5A and NS5B polymerase inhibitors or entry inhibitors), as well as non-specific antivirals [1–5]. The available drugs in 2016 are from a second generation of NS5B polymerase inhibitors (sofosbuvir, dasabuvir), protease inhibitors (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 for approval and usage 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]. However, there is little data regarding the sofosbuvir + daclatasvir combination in genotype 1-infected patients.

We report the first real-life results of the France REcherche Nord&Sud Sida-hiv Hépatites (ANRS) CO22 HEPATHER cohort (Therapeutic options for hepatitis B and C: A French cohort) for the sofosbuvir + daclatasvir combination in genotype 1-infected patients.

Patients and methods

Study design and participants

The 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, who were most likely improve in 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. These patients were 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 "Comité de Protection des Personnes (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 urine samples were collected and stored in a centralized biobank (Cell&Co Biorepository, Pont du Château, France). Combined systematic follow-up visits (1/year) and spontaneous reports on dedicated forms for particular events (e.g., deaths, hepatocellular carcinoma, start of therapy) were completed. In April 2014, specific instructions were given to the centres to prioritize the inclusion of patients with chronic hepatitis C, who were to 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 (W)1, 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 the physicians' discretion.

By September 8th 2015, 13,832 HCV-positive patients had been included in the cohort, of which 4836 patients were given a treatment including at least one DAA and of these 4459 received an interferon (IFN)-free regimen. We selected all patients with HCV genotype 1 infection who initiated a combination of sofosbuvir (400 mg/day) and daclatasvir (60 mg/day) with or without ribavirin (1–1.2 g/day) before October 1st 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 $\geqslant$12.5 kPa by FibroScan® and/or a FibroTest® result $\geqslant$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 absence of detectable HCV-RNA 12 weeks after the last treatment intake. Secondary endpoints were the absence of detectable HCV-RNA 4 weeks after last treatment intake (SVR4), premature treatment discontinuation and adverse events.