Hepatitis C treatment with all-oral direct-acting antivirals: Effectiveness and tolerance in a multicenter, prospective, observational study from French general hospitals (APROVVIE, ANGH)

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Summary

Background and aims > According to clinical trials, the treatment of patients with chronic hepatitis C (CHC) with second-generation direct acting antiviral agents (DAAs) is highly efficient and well tolerated. The goal of this study was to investigate the effectiveness and safety of various combinations of these drugs during their first 2 years of use in the real-world practice of French general hospitals.

Methods > Data from patients treated with all-oral DAAs in 24 French non-academic hospital centers from March 1, 2014 to January 1, 2016, were prospectively recorded. The sustained virological response 12-24 weeks after treatment (SVR 12-24) was estimated and severe adverse events (SAE) were evaluated and their predictive factors were determined using logistic regression.

Results > Data from 1123 patients were analyzed. The population was 69% genotype (G) 1, 13% G3, 11.5% G4, 5% G2, 49% with cirrhosis and 55% treatment-experienced. The treatment regimens were sofosbuvir/ledipasvir (38%), sofosbuvir/daclatasvir (32%), sofosbuvir/ribavirin (18%), ombitasvir + paritaprevir + ritonavir (5%) (with dasabuvir 3.5%), and sofosbuvir/ribavirin (8%). Ribavirin was given to 24% of patients. The SVR 12-24 was 91.0% (95% CI: 89.2–92.5%). Sofosbuvir-ribavirin was less effective than other regimens. The independent predictors of SVR 12-24 by logistic regression were body weight, albumin, previous hepatocellular carcinoma and treatment regimen (sofosbuvir/ribavirin vs. others). Sixty-four severe adverse events (SAE) were observed in 59 [5.6%] patients, and were independently predicted by cirrhosis and baseline hemoglobin. Serum creatinine increased during treatment (mean 8.5%, [P < 10⁻⁵]), satisfying criteria for acute kidney injury in 62 patients (7.3%). Patient-reported overall tolerance was excellent, and patient-reported fatigue decreased during and after treatment.

Conclusions > Second generation DAAs combinations are as effective and well tolerated in a « real-world » population as in clinical trials. Further studies are needed on renal tolerance.

Résumé

Traitement de l’hépatite chronique C par une combinaison orale de nouveaux antiviraux directs : efficacité et tolérance dans la vraie vie dans la cohorte APROVVIE de l’ANGH

Objectif > Les essais thérapeutiques des antiviraux d’action directe (AAD) de seconde génération ont montré leur efficacité et leur bonne tolérance. Nous avons voulu évaluer l’efficacité et la tolérance de diverses combinaisons de ces médicaments pendant leurs deux premières années d’utilisation dans la pratique quotidienne d’hôpitaux généraux français.

Méthodes > Les données des malades traités avec des DAA sans interféron dans 24 centres hospitaliers non universitaires entre le 1er mars 2014 et le 1er janvier 2016 ont été enregistrées...
Direct-acting antivirals (DAAs) have revolutionized the treatment of patients with chronic hepatitis C (CHC). Second-generation DAAs are now given without interferon (IFN) and clinical trials have shown these treatments to be highly effective with excellent tolerance. Real world, post-marketing studies are important. Previous studies have shown that treatment with the combination of IFN and ribavirin (RBV), then pegylated IFN and RBV, and later of pegylated IFN, RBV and boceprevir or telaprevir resulted in lower sustained virological response (SVR) rates and a higher rate of severe adverse events (SAE) rates than in phase III trials [1-3]. These discrepancies were probably due to the characteristics of the populations treated in real-world studies with a higher proportion of patients who were elderly or with cirrhosis and, in American studies, with more African Americans, as well as adherence to treatment, and drug-drug interactions [3]. Post-marketing observational studies can provide information about questions that were not included in initial clinical trials (i.e. ideal duration of treatment, combinations of drugs from different pharmaceutical companies, comparative effectiveness studies of drug combinations marketed by different companies) as well as report SAE and long-term follow-up outcomes. [3] Results of post-marketing observational studies can more reliably be generalized from the study to the general population than clinical trials. This study evaluated the effectiveness and tolerance to all-oral DAAs regimens during the first two years after they became available in a large French population of patients with CHC treated in general (non-academic) hospitals.

Methods
APROVVIE is a multicenter observational study performed by the Association nationale des gastroentérologues des hôpitaux généraux (ANGH) in French general hospitals that registers all consecutive adult (> 18 years old) patients treated for CHC and evaluates the efficacy and tolerance of treatment in a post-marketing setting. The study began on October 10, 2012. Investigators began including patients treated with new DAAs on July 4, 2014, first in early access programs, and then in current practice. The protocol was performed in accordance with the Declaration of Helsinki and French Law for Biomedical Research, and authorized by the Commission nationale de l'informatique et des libertés (Decision DR-2012-298). Written informed consent was obtained from each patient. The main patient characteristics (age, gender, body weight [but not height], previous treatment and response, cirrhosis, Child-Pugh score, previous hepatocellular carcinoma, viral genotype, baseline viral load, extra-hepatic manifestations, comorbidities, other treatments, alcohol use, opioid substitution, listing for liver transplantation, HIV and HBV status, hemoglobin, platelets, prothrombin time, creatinine, albumin, bilirubin, treatment combinations) and the follow-up results were recorded by the investigators on an electronic case-report form (CRF). There were no follow-up data beyond the evaluation of results after 12 and/or 24 weeks of DAAs treatment. The diagnosis of cirrhosis was made by liver biopsy or one of the non-invasive tests, Fibrotest® Fibroscan® or Fibrometer® at the discretion of the investigators, according to French
recommendations [4]. Baseline concomitant comorbidities and medications were recorded for each patient. Standard laboratory tests (including hematological tests, and routine biochemical tests) were performed locally.

Virological techniques
Blood HCV-RNA was determined by COBAS AmpliPrep®/COBAS TaqMan® (Roche Molecular Systems, Pleasanton, California, USA), or with Abbott Real Time HCV Assay (Abbott Molecular, Des Moines, Illinois, USA), with a lower limit of detection of 15 IU/mL and 12 IU/mL, respectively. A sustained virological response (SVR) was defined as undetectable HCV-RNA at least 12 weeks after the end of treatment. A virological relapse was defined as detectable HCV-RNA after HCV-RNA had become undetectable at the end of treatment. A virological breakthrough was defined as an increase of at least one log IU/mL from the nadir HCV-RNA level or recurrence of HCV-RNA after it became undetectable during treatment.

Tolerance, adverse effects and fatigue.
Only adverse effects > grade 2 according to Common Terminology Criteria for Adverse Events, version 4.1, were recorded [5]. Overall tolerance was assessed by a visual analog scale for each patient at the beginning and end of treatment. Fatigue was also assessed by visual analog scale for each patient at the beginning, end, and 2–6 months after the end of treatment. Estimated glomerular filtration rate (eGFR) was assessed using the MDRD formula; maximum serum creatinine observed during treatment was noted by each investigator at the end of the treatment period, and the occurrence of acute kidney failure was then determined based on a threshold of an increase in serum creatinine 1.5–1.9 times from baseline or a ≥26.5 μmol/L increase [6].

Treatments
Drugs were prescribed at the discretion of each investigator. Treatment schedules proposed by the Association française pour l'étude du foie, which were regularly updated on its website, were recommended to investigators [7].

Statistical analysis
Continuous variables were compared using the Student t-test or the Mann–Whitney U test, a paired-test for paired variables comparisons. The Fisher’s exact test or the Chi² test was used to analyze categorical variables. Factors associated with SVR (P < 0.10) on univariate analysis were entered into a multiple logistic regression model. Calculations were performed using NCSS 9 statistical software (Kaysville, Utah, USA, www.ncss.com).

The number of patients required was not predetermined. The investigators consecutively included all patients treated during the study period. STROBE statements were respected [8].

Results
Description of the population
Between March 1, 2014, and January 1, 2016, 1334 patients were included. There were 4 duplicates, 10 never began their treatment, 98 received interferon, and data was incomplete in 99 due to incomplete records or because their physician left the study. Thus, 1123 patients were evaluated. The main patient characteristics are reported in table 1. At the beginning of treatment, the median age was 56 years old (IQR 14, (18–89)), and 62% of patients were men. Genotype 1 was predominant (68.7%)-1b in 51.9% of cases, followed by genotypes 3 (13.3%), 4 (11.5%) and 2 (4.6%). Fifty-five percent of patients were treatment-experienced, 128 (20.7%) with telaprevir or boceprevir. Cirrhosis was present in 553 (49.2%) patients and was compensated in 40 (7.2%). There were 455 patients (86.8%) with Child-Pugh Class A cirrhosis and 228 (44.2%) with esophageal varices. Hepatocellular carcinoma was previously diagnosed in 24 patients (2.2%). HIV infection was present in 99 (8.8%) patients, and 8 (0.7%) patients were HBsAg positive. Two-thirds of patients had comorbidities, with a mean 1.75 comorbidities per patient (table I and supplementary table I), and 63.3% took at least one drug daily before beginning hepatitis treatment. Two hundred and forty-one (22.4%) patients used alcohol and 124 (11.5%) patients took opioid substitutes. IFN-free combinations varied depending upon the availability of drugs and changing guidelines: 426 (37.8%) received sofosbuvir and ledipasvir (LDV/SOF) + 0 RBV, 358 (31.8%) sofosbuvir and daclatasvir + 0 RBV, 190 (16.9%) sofosbuvir and simprevir (SOF/SIM), 89 (7.8%) SOF/RBV, 39 (3.5%) the PRD combination of ritonavir-boosted paritaprevir with ombitasvir and dasabuvir (PTV/OBV+ DSV)+/0 RBV, and 20 (1.8%) the PR combination (PTV/OBV + RBV). Overall, 270 (24.0%) patients received weight-based RBV. Drug combinations according to genotype are indicated in table I.

Efficacy analysis
Sustained virological response
The overall SVR rate was 91.0% (95% CI: 89.2–92.5). The SVR rates according to genotype and drug regimens are indicated in table II.

The SVR rates in patients with cirrhosis (according to genotype and drug combination), are indicated in table III. The SVR rate was 405/456 (89.0%), 51/60 (85.0%), and 6/9 (66.7%) in Child-Pugh A, B and C patients, respectively.

Treatment failure was observed in 100 patients: 58 relapses, 5 breakthrough/non responses, 13 SAEs, 1 premature treatment discontinuation by the patient, and 23 lost to follow-up.

Factors associated with SVR 12-24
The factors associated with SVR 12-24 on univariate analysis were weight, cirrhosis, previous hepatocellular carcinoma, hemoglobin, platelet count, prothrombin time, albumin, ribavirin use (a negative relationship, which disappeared when the analysis was
### Table 1

**Main characteristics of the 1123 patients studied**

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>G 1</th>
<th>G 2</th>
<th>G 3</th>
<th>G 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n (%)</td>
<td>1123 (100)</td>
<td>771 (68.7)</td>
<td>52 (4.6)</td>
<td>149 (13.3)</td>
<td>129 (11.5)</td>
</tr>
<tr>
<td>Age (years): median (IQR)</td>
<td>56 (14)</td>
<td>57 (16)</td>
<td>65.5 (16)</td>
<td>54.0 (9.0)</td>
<td>55.0 (9.5)</td>
</tr>
<tr>
<td>Male gender: n (%)</td>
<td>698 (62.2)</td>
<td>474 (61.4)</td>
<td>27 (51.9)</td>
<td>110 (73.8)</td>
<td>75 (58.1)</td>
</tr>
<tr>
<td>Weight (kg): median (IQR)</td>
<td>71 (18)</td>
<td>74 (18.5)</td>
<td>70.5 (20.8)</td>
<td>75.0 (19.5)</td>
<td></td>
</tr>
<tr>
<td>Treatment naïve: n (%)</td>
<td>506 (45.1)</td>
<td>340 (44.1)</td>
<td>30 (57.7)</td>
<td>72 (48.3)</td>
<td>53 (43.1)</td>
</tr>
<tr>
<td>Previous non-responder: n (%)</td>
<td>293 (26.1)</td>
<td>218 (28.3)</td>
<td>3 (5.8)</td>
<td>28 (18.8)</td>
<td>41 (31.8)</td>
</tr>
<tr>
<td>Previous relapser: n (%)</td>
<td>261 (23.2)</td>
<td>173 (22.4)</td>
<td>18 (34.6)</td>
<td>38 (25.5)</td>
<td>26 (20.2)</td>
</tr>
<tr>
<td>Cirrhosis: n (%)</td>
<td>553 (49.2)</td>
<td>378 (49.0)</td>
<td>24 (46.2)</td>
<td>87 (58.4)</td>
<td>56 (43.4)</td>
</tr>
<tr>
<td>Child-Pugh A/B/C (n)</td>
<td>455/60/9</td>
<td>300/48/5</td>
<td>22/01/01</td>
<td>47/9/2</td>
<td>51/2/1</td>
</tr>
<tr>
<td>F3 fibrosis: n (%)</td>
<td>354 (31.5)</td>
<td>236 (30.6)</td>
<td>15 (28.8)</td>
<td>39 (26.2)</td>
<td>36 (27.9)</td>
</tr>
<tr>
<td>Past history of hepatocellular carcinoma: n (%)</td>
<td>24 (2.2)</td>
<td>15 (2.0)</td>
<td>2 (3.9)</td>
<td>4 (2.7)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>HCV Viral load &gt; 800,000 UI/mL: n (%)</td>
<td>727/1104 (65.8)</td>
<td>506/757 (66.8)</td>
<td>31 (59.6)</td>
<td>94 (64.4)</td>
<td>80 (63.0)</td>
</tr>
<tr>
<td>Genotype 1a: n</td>
<td>330</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Genotype 1b: n</td>
<td>400</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 5: n</td>
<td>18 (1.6)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Genotype 6: n</td>
<td>4 (0.4)</td>
<td></td>
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<tr>
<td>Anti-HIV-positive: n (%)</td>
<td>99 (8.8)</td>
<td>63 (8.2)</td>
<td>1 (1.9)</td>
<td>13 (8.7)</td>
<td>22 (17.1)</td>
</tr>
<tr>
<td>HBsAg-positive: n (%)</td>
<td>8 (0.7)</td>
<td>4 (0.5)</td>
<td>1 (1.9)</td>
<td>1 (0.7)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Platelets giga/L: median (IQR)</td>
<td>172 (95)</td>
<td>171.5 (960)</td>
<td>179 (100)</td>
<td>170 (91.5)</td>
<td>179 (95.)</td>
</tr>
<tr>
<td>Prothrombin time %: median (IQR)</td>
<td>93 (17)</td>
<td>93.0 (16.0)</td>
<td>91.0 (17.3)</td>
<td>90.0 (18.0)</td>
<td>94.0 (15.5)</td>
</tr>
<tr>
<td>Albumin g/L:median (IQR)</td>
<td>40 (6)</td>
<td>39.6 (6.0)</td>
<td>42.0 (8.5)</td>
<td>40.0 (6.0)</td>
<td>40.0 (5.0)</td>
</tr>
<tr>
<td>Patients with comorbidities: n (%)</td>
<td>695/1050 (66.3)</td>
<td>484/720 (67.2)</td>
<td>37/48 (77.1)</td>
<td>78 (55.7)</td>
<td>84 (67.7)</td>
</tr>
<tr>
<td>Patients taking other treatments: n (%)</td>
<td>711 (63.3)</td>
<td>484/771 (62.8)</td>
<td>38 (73.1)</td>
<td>87 (58.4)</td>
<td>90 (69.8)</td>
</tr>
<tr>
<td>SOF + SIM (+/0 RBV): n (%)</td>
<td>190 (16.9)</td>
<td>150 (19.5)</td>
<td>1 (1.9)</td>
<td>1 (0.7)</td>
<td>38 (29.5)</td>
</tr>
<tr>
<td>SOF + DCV (+/0 RBV): n (%)</td>
<td>358 (31.8)</td>
<td>202 (28.50)</td>
<td>10 (19.2)</td>
<td>117 (78.5)</td>
<td>19 (14.7)</td>
</tr>
<tr>
<td>SOF + SIM + DCV</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SOF + RBV: n (%)</td>
<td>89 (7.8)</td>
<td>22 (2.9)</td>
<td>39 (75.0)</td>
<td>20 (13.4)</td>
<td>7 (5.4)</td>
</tr>
<tr>
<td>SOF + LDV (+/0 RBV): n (%)</td>
<td>426 (37.8)</td>
<td>357 (46.3)</td>
<td>2 (3.8)</td>
<td>11 (7.4)</td>
<td>45 (34.9)</td>
</tr>
<tr>
<td>OBV + PTV + RTV: n (%)</td>
<td>59 (5.3)</td>
<td>39 (5.1)</td>
<td>0</td>
<td>0</td>
<td>20 (15.5)</td>
</tr>
<tr>
<td>+ DSV: n (%)</td>
<td>39 (3.5)</td>
<td>38 (4.9)</td>
<td>0</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>RBV</td>
<td>270 (24.0)</td>
<td>121 (15.7)</td>
<td>42 (80.8)</td>
<td>67 (45.0)</td>
<td>38 (29.5)</td>
</tr>
<tr>
<td>Duration of treatment in weeks: mean (SD)</td>
<td>15.6 ± 5.6</td>
<td>15.0 (5.4)</td>
<td>12.7 (2.7)</td>
<td>20.7 (5.6)</td>
<td>14.0 (4.6)</td>
</tr>
</tbody>
</table>

G: genotype; SOF: sofosbuvir; RBV: ribavirin; SIM: simeprevir; DCV: daclatasvir; LDV: ledipasvir; OBV: obinatavir; PTV: paritaprevir; RTV: ritonavir; DSV: dasabuvir.
limited to patients not treated with SOF/RIBA alone) and the treatment combination (SOF/RBV vs. other treatments) (Table IV). There was no significant difference between patients who did or did not achieve an SVR for age, gender, previous treatment status (experienced or not), the presence and number of comorbidities, alcohol use, cannabis use, opioid substitution, treatment duration or organized patient education.

Logistic regression analysis identified 4 independent predictors of SVR: body weight, previous hepatocellular carcinoma, albumin and treatment combination (SOF/SIM, SOF/DCV and SOF/LDV were better than SOF/RBV alone).

In the 553 patients with cirrhosis, the factors associated with SVR 12-24 on univariate analysis were previous decompensation of cirrhosis, previous hepatocellular carcinoma, hemoglobin level, prothrombin time, serum albumin level and treatment combination. Logistic regression analysis only identified previous hepatocellular carcinoma as an independent predictor of SVR (OR: 0.22 [95% CI: 0.09-0.58], P = 0.002) and treatment
combination (SOF/DCV: OR 3.39 [95% CI: 1.38-8.31], \( P = 0.008 \)) and SOF/LDV: OR 2.39 [95% CI:0.98-5.88], \( P = 0.06 \)).

### Tolerance and adverse events

Self-assessed overall tolerance was excellent (median: 8/10, IQR: 2.0) and better in patients who did not receive ribavirin than in those who did (mean ± SD: 8.2 ± 1.6 vs. 7.5 ± 1.9, \( P < 10^{-5} \)). Self-assessed fatigue was similar at the beginning of treatment and decreased significantly during and even more after the end of treatment (figure 1), with no difference between patients receiving or not receiving ribavirin.

An adverse event greater than grade 2 severity was observed in 59 (5.6%) patients for a total of 65 SAEs (supplementary table II). The frequency of SAE was similar in patients treated with SOF/SIM (6.6%), SOF/DCV (4.6%) and SOF/LDV (4.8%), and in patients receiving or not sofosbuvir (5.2% vs. 3.4%, respectively, \( P = 0.76 \)) but was greater in patients treated with ribavirin (8.5% vs. 4.6%, \( P = 0.02 \)). There were 9 deaths, all in patients with cirrhosis (3 from hepatocellular carcinoma, 2 from decompensation and 1 from cardiac failure, renal failure, fulminant undifferentiated carcinoma and septic shock, respectively).

Three of the patients treated with sofosbuvir presented with bradyarrhythmia, none receiving amiodarone, but two who had previously been treated with beta-blockers, and two patients with cirrhosis (receiving sofosbuvir and daclatasvir) developed pulmonary hypertension. One patient, who stopped flecainide treatment for atrial fibrillation before beginning sofosbuvir-based treatment, had a relapse of arrhythmia complicated by embolic stroke. Details of cardiovascular SAE are given in supplementary table II.

The median decrease in hemoglobin was significantly different from zero and was 0.8 g/dL (IQR 1.7). The median decrease in

| Table IV: Uni- and multivariate analysis of factors associated with SVR 12-24 in the whole cohort |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Body weight kg:** mean ± SD | 72.4 ± 0.7 vs. 73.6 ± 1.8 | 0.66 | 0.002 | 0.77 (0.44-1.36) | 0.37 |
| **Cirrhosis:** n (%) | 489/553 (88.4) vs. 534/570 (93.7) | 0.52 (0.34-0.79) | 0.002 | 7.5 (5.4-10.3) | 0.37 |
| **Previous decompensation:** n (%) | 31/40 (77.5) vs. 458/513 (89.3) | 0.41 (0.19-0.90) | 0.05 | 9.0 (4.3-19.3) | 0.37 |
| **Previous Hepatocellular carcinoma** | 15/24 (72.4) vs. 474/529 (89.6) | 0.19 (0.08-0.45) | 0.02 | 0.22 (0.09-0.58) | 0.002 |
| **Hb:** g/dL (mean ± SEM) | 14.2 ± 0.1 vs. 13.6 ± 0.2 | 1.16 (1.03-1.32) | 0.01 | 1.10 (0.93-1.31) | 0.25 |
| **Prothrombin time:** % (mean ± SEM) | 84.6 ± 0.8 vs. 79.2 ± 2.1 | 1.02 (1.00-1.03) | 0.01 | 1.00 (0.98-1.02) | 0.82 |
| **Albumin:** g/L (mean ± SEM) | 38.4 ± 0.3 vs. 35.7 ± 0.7 | 1.08 (1.03-1.13) | 0.001 | 1.06 (0.99-1.12) | 0.09 |
| **Treatment combination** | 0.002 | | | | |
| **SOF/SIM vs. SOF/RIB** | 77/91 (84.6) vs. 35/47 (74.5) | 1.89 (0.80-4.44) | 0.15 | 1.19 (0.46-3.07) | 0.72 |
| **SOF/DCV vs. SOF/RIB** | 205/221 (92.8) vs. 35/47 (74.5) | 4.39 (1.94-9.95) | 0.0002 | 3.39 (1.38-8.31) | 0.007 |
| **SOF/LDV vs. SOF/RIB** | 158/176 (89.8) vs. 5/47 (74.5) | 3.01 (1.35-6.74) | 0.006 | 2.39 (0.98-5.88) | 0.06 |
| **OMB/PAR/RITO/ + DASO vs. SOF/RIB** | 14/18 (77.8) vs. 5/47 (74.5) | 1.20 (0.34-4.12) | 0.78 | 0.85 (0.19-3.73) | 0.83 |

Hb: hemoglobin; G: genotype; SVR: sustained virological response; SOF: sofosbuvir; RBV: ribavirin; SIM: simeprevir; DCV: daclatasvir; LDV: ledipasvir; PTD: PTV/OMV + RBV; PRTD: ritonavir-boosted paritaprevir with ombitasvir and dasabuvir.

\(^1\)Sof 12-24 vs. No SVR 12-24.

\(^2\)Sof 12-24 with vs. without.

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**Figure 1:** Self-assessed fatigue before, at the end, and 36 months after the end of treatment.
hemoglobin was greater in patients receiving, than in those not receiving, ribavirin (2.2 g/dL, IQR 2.5 vs. 0.6 g/dL, IQR 1.2) \((P < 10^{-5})\).

Baseline serum creatinine and maximum serum creatinine during antiviral treatment were available in 855 patients. Serum creatinine increased from 73.4 ± 36.1 to 79.7 ± 37.5 μmol/L \((P < 10^{-5})\), 95% CI of the difference: 4.7-7.8 mL/min. There was no significant correlation between the variation in serum creatinine and age, sex, the presence of cirrhosis, diabetes, arterial hypertension, baseline serum creatinine or sofosbuvir-containing treatment. These measures were only available in 35 patients not receiving sofosbuvir. The 95% CI of the difference was -3.2 to +12.1 mL/min \((P = 0.25)\). We had no data about the later course. An increase in serum creatinine \(\geq 26.5\) μmol/L \(\geq 150\%\) of the baseline value (the threshold criteria for AKI stage I \([6]\)) was observed in 62 (7.3%) patients (mean age 59 years old, 40 men, 41 with cirrhosis, all but one treated with sofosbuvir). The presence of type 2 diabetes, cirrhosis and serum albumin were significant predictive factors in univariate analysis, but not the age, the presence of arterial hypertension, or treatment with sofosbuvir. Only type 2 diabetes (OR: 2.73, 95% CI: 1.41-5.25, \(P = 0.003\)) and serum albumin (OR: 0.91; 95% CI: 0.87-0.96, \(P = 0.0003\)) remained independent predictive factors in logistic regression analysis. Overall, univariate analysis showed that the factors significantly associated with more than one grade 2 adverse event were cirrhosis (9.2% vs. 1.9%, \(P = 2.10^{-5}\)), hepatocellular carcinoma (25.0% vs. 5%, \(P = 2.10^{-5}\)), the presence of comorbidities (6.8% vs. 3.5%, \(P = 0.03\)), the use of ribavirin (8.5% vs. 4.2%, \(P = 0.007\)), the type of combination therapy (\(P = 0.06\)), baseline hemoglobin (13.3 vs. 14.4 g/dL, \(P = 10^{-5}\)), neutrophils (\(P = 0.05\)), platelets (\(P = 0.0002\)), albumin (\(P = 0.0001\)) and bilirubin (\(P = 0.0007\)). The independent predictive factors of grade 2 or higher adverse events were the presence of cirrhosis (OR 3.23; 95% CI: 1.41-7.38, \(P = 0.005\)) and baseline hemoglobin (OR 0.81; 95% CI: 0.69-0.97, \(P = 0.01\)).

**Special populations**

Renal failure (eGFR < 60/mL/min) was present in 64 patients (30 [46.9%] with cirrhosis, mean age 65.5 years old); 62 of these (96.9%) achieved SVR 12-24 (\(P = 0.08\) vs. patients with no renal failure). Seven (10.9%) had severe adverse events (anemia requiring blood transfusion and/or erythropoietin treatment in four patients, acute renal failure, septic shock, and transient ischemic attack in one patient each) \((P = 0.08\) vs. patients with no renal failure), and 2 died (both had uncompensated cirrhosis). One patient treated with sofosbuvir and daclatasvir died of acute renal failure associated with terminal liver failure despite liver transplantation, the other treated with sofosbuvir and simprevir died with septic shock. An increase in serum creatinine \(\geq 26.5\) μmol/L \(\geq 150\%\) of basal value was observed in 14/52 patients with renal failure vs. 47/803 without \((P < 10^{-5})\). Details of SAE observed in patients with renal failure are given in supplementary table III.

Ninety-nine patients had HIV co-infection (32 [32.3%] with cirrhosis), (96 [97.0%, 95% CI: 93.6-100) of whom achieved SVR 12-24. Three patients (3.3%) had SAE and none died.

**Discussion**

**Summary of results**

In our study performed in more than 1000 patients with chronic hepatitis C, half with cirrhosis, treated in specialized units in non-academic French hospitals, the use of all oral second-generation DAAs with or without ribavirin was highly effective, with a global SVR rate of 91%. The association of sofosbuvir and ribavirin, the first interferon-free combination that became available on the market, was less effective than the others. The objective tolerance was good, with a relatively low rate of severe adverse effects (less than 6%), which seemed to be mainly associated with the severity of liver disease rather than the drugs used (except for ribavirin). SAE were independently predicted by the presence of cirrhosis and baseline hemoglobin. However, an unexplained and slight deterioration in renal function was observed in our study. Subjective tolerance was excellent, and self-assessed fatigue decreased during and after the cessation of treatment.

**What they add to the knowledge (Comparison with literature)**

Clinical trials have reported excellent results on the efficacy and tolerance to DAAs. Our results, like others, \([9]\) suggest that these excellent results can be extended to large cohorts of patients treated in real-life conditions. Because national authorities initially limited the use of these regimens to severe patients, mostly prior treatment failures or with contra-indications to interferon, poorer outcomes might have been expected, such as those with interferon-ribavirin and later with the first-generation DAAs, boceprevir and telaprevir. It is now clear that this hypothesis was unfounded and the efficacy observed in “real-world” studies \([9-11]\) supports those of clinical trials. The results of SOF/DCV and SOF/LDV were similar in the 771 patients with genotype 1 virus in our study and slightly better than SOF/SIME, which was used early in the study. The mean SVR 12-24 rate in 13,073 genotype 1 patients treated with SOF/LDV in 11 other “real-world” studies was 94.3% (95% CI: 94.0-94.7) in the entire population, and 91.7% (90.8-92.6) in 3,506 patients with cirrhosis. These results are comparable to ours \([10]\).

The SVR rates in the 151 patients with genotypes 4, 5 and 6 in our study were nearly identical to those in genotype 1 patients with the same combinations. This is consistent to results in the literature \([12]\).
One hundred seventeen out of 149 patients with genotype 3 in our study received SOF/DCV; 70% alone for 24 weeks and 34% in association with RBV with a mean SVR of 88% (80.0–92.7). This is very similar to the rate reported by Hezode at al. in the first French patients treated in the initial compassionate use program [13]. The SVR was lower in patients with cirrhosis (82.6% vs. 95.8%, p = 0.03). Ribavirin and 24 weeks of treatment were not shown to increase the efficacy in patients with cirrhosis in our study, although this was strongly suggested in a recent network meta-analysis [11].

Only 52 patients with genotype 2 were treated in our study. The SVR rate was higher in the 13 treated with SOF/DCV, SOF/SIM or SOF/LDV (100%) than in the 39 treated with SOF/RBV alone (79.5%), p = 0.06.

The independent predictors of SVR were body weight, previous hepatocellular carcinoma, albumin and treatment combination. Cirrhosis was not a predictor of SVR, probably because most of our patients were Child A. Unlike interferon-based treatments, body weight is not usually a negative predictive factor of SVR with DAAs treatment. In our study, the body weight distribution was normal and the limits of the 25-75th percentiles were 61 and 80 kg. We did not measure BMI.

SAE were rare (5.6%), and more frequent in patients who received RBV, although logistic regression only identified cirrhosis and baseline hemoglobin as independent predictive factors of SAE. SAE were the cause of 13% of treatment failures. SAE occurred in no more than 6% of patients with genotype 1 virus, and treatment was only discontinued due to adverse events in 0.8-2.3% [11]. Cardiovascular effects were the most frequent. We observed three cases of bradycardia in patients receiving sofosbuvir-based treatment, none receiving amiodarone, but two of these were receiving beta-blockers [14]. There was one case of atrial fibrillation relapse complicated by embolic stroke following the unwarranted withdrawal of flecainamide before starting sofosbuvir (hep-druginteractions.com). This illustrates potential bidirectional errors concerning DAAs drug interactions. We observed the apparent onset of pulmonary hypertension in two patients with cirrhosis during sofosbuvir-based treatment. This has been observed in a few cases, including one from our group [15], and the relationship with antiviral treatment has not been clarified.

The efficacy and tolerance were similar in 99 patients with HIV infection. Efficacy was high, but tolerance tended to be lower in patients (all with cirrhosis) with renal failure. Similar results have been recently reported in a large prospective Spanish registry [16].

We observed a slight but significant increase in serum creatinine (mean 8.5%) in the 855 patients who had at least one serum creatinine measurement during antiviral treatment. We did find an explanation for this, and unfortunately there were no results of specialized renal investigations or follow-up data. A similar unexpected increase in serum creatinine was observed in a series of 43 Chinese patients treated with sofosbuvir-containing treatment. Twenty-four weeks after the end of treatment, the increase in serum creatinine only reversed in non-cirrhotic patients [17]. Although the efficacy of antiviral treatment in patients with existing renal failure was excellent, there was a tendency towards an increase in SAE (anemia in particular) and worsening of renal dysfunction, as previously described in the HCV-TARGET study [18]. Close monitoring is clearly indicated in these patients, and, when possible, alternative, sofosbuvir-free, combinations should be used, at least in patients with severe renal failure [19].

Self-assessed overall tolerance to treatment was excellent. Self-assessed fatigue decreased during treatment and further decreased 3 to 6 months after the end of treatment. In contrast, in our previous experience, fatigue persisted during treatment in the 66 patients treated with peginterferon, sofosbuvir and ribavirin, then significantly decreased 3–6 months after the end of treatment (unpublished observations). These observations confirm those in studies that have specifically evaluated quality of life [20].

**Strengths and limitations**

The main strength of this study is that it included a large, unselected population with no specific exclusion criteria, studied under real-life conditions outside university hospitals, with all genotypes and all available drug combinations, to provide objective results on efficacy and tolerance as well as patient-reported outcomes on the course of fatigue and overall tolerance. The main limitations of our study are its observational design and electronic data collection. This could result in a potential physician-prescribing bias, incomplete records, local practice discrepancies, data entry errors, and missing data. Finally, we had no long-term follow-up data.

**Implications of results**

Our results show that the results from phase III studies are largely applicable to real-life conditions, and suggest that the management of CHC treatment could be transferred from tertiary centers to community-based non specialists [21], at least in patients without HIV or HBV coinfection, severe renal failure, severe liver disease or previous antiviral treatment [19] as long as a detailed work-up of liver disease, comorbidities and potential drug interactions is performed [19].

**Future research**

This period has clearly been a revolution for previously treated patients and their physicians. In the future, real-life studies are still needed to identify the most cost-effective combinations and treatment durations, including for newer drug combinations such as sofosbuvir/velpatasvir/voxilaprevir and glecaprevir/pibrentasvir. Despite the excellent overall tolerance, the safety of these treatments should be studied in more detail, in particular concerning renal function.

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