Sofosbuvir-Daclatasvir-Simeprevir plus Ribavirin in Direct-Acting Antiviral-Experienced Hepatitis C Patients

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Abstract

We assessed the broadly-used, off-label combination of sofosbuvir, daclatasvir, simeprevir and ribavirin in DAA-experienced patients, as recommended in current guidelines despite scarce data. After 24 weeks' treatment, six patients (60%) achieved sustained virologic response at 12 weeks. Two cirrhotic patients relapsed and two discontinued treatment due to serious adverse events.

Keywords: chronic hepatitis C; retreatment; sustained virological response; resistance; resistance-associated substitutions

All-oral, interferon-free, direct-acting antiviral (DAA)-based combination regimens are the new standard-of-care across a variety of settings, as recommended by international liver societies [1, 2]. Sustained virological response (SVR) rates typically exceed 90% in treatment-naïve patients infected with HCV genotype 1 or 4 treated with two or more DAAs [3–7]. Treatment failure and selection of resistant variants are influenced by several parameters, including viral factors (HCV [hepatitis C virus] genotype, fitness of resistant variants), host factors (fibrosis stage, portal hypertension), and treatment-related factors (therapy adherence, DAA metabolism, concomitant use of ribavirin, treatment duration) [3, 8–10].

Current options for relapsing patients after a DAA-containing regimen are limited and supportive evidence is lacking. EASL Recommendations 2016 recommend that retreatment be based on an interferon-free combination, including sofosbuvir as a backbone (because of its higher barrier to resistance than other agents), plus one to three other DAAs, ideally with no cross-resistance with the previously administered drugs, plus ribavirin for 12–24 weeks (24 weeks in patients with an F3 or F4 METAVIR fibrosis score) [1].

We report a prospective, open-label, "real-world" study, aimed at evaluating the efficacy and safety of sofosbuvir, daclatasvir, and simeprevir with ribavirin in chronically infected patients who failed prior treatment.

METHODS

Patients and treatment

Ten consecutive patients who previously relapsed after treatment with an all-oral DAA-based combination regimen administered for 12 weeks without ribavirin were included; all were also enrolled in the ANRS CO22 HEPATHER cohort [6] and in the French National Observatory for HCV Resistance to Antiviral Drugs, and provided written informed consent.

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in *a priori* approval by the ethics committee "Ile de France III".

Patients were treated for 24 weeks with a combination of sofosbuvir 400 mg, daclatasvir 60 mg, and simeprevir 150 mg with weight-based ribavirin 1000–1200 mg/day.

Assessments

Safety and tolerability were assessed monthly and included regular physical examinations, adverse event assessment, and clinical laboratory blood sample testing.

HCV RNA levels were measured using the Abbott RealTi*me* HCV assay (Abbott Molecular, Des Plaines, IL) with an identical lower limit of quantification and detection of 12 IU/mL (1.1 Log IU/mL). Antiviral efficacy was assessed by measuring HCV RNA levels at baseline and at Weeks 4, 8, 12, 16, 20, and 24 (end-of-treatment [EOT]), and at 4 and 12-weeks post-treatment. The main efficacy endpoints were the on-treatment virological responses (HCV RNA <12 IU/mL) and SVR (HCV RNA <12 IU/mL) 12 weeks after the EOT (SVR12) [11].

The presence of resistance-associated substitutions (RASs) was assessed in all patients prior to retreatment (retreatment baseline) and post-treatment in those who failed to achieve SVR12, as well as in any patient discontinuing prematurely. HCV resistance analysis was based on population sequencing of the regions coding for the NS3/4A protease (targeted by simeprevir), the NS5A protein (targeted by daclatasvir), and the NS5B polymerase (targeted by sofosbuvir), as previously described [12].

Statistical Analyses

Descriptive results are presented as mean ± standard deviation or median with interquartile range for continuous data, and number (percentage) for categorical data. No formal statistical analyses were undertaken.

RESULTS

Patients

Eight of the 10 re-treated patients completed treatment. The median time between the end of prior DAA treatment and initiation of retreatment was 14 months (range 5–28). Baseline characteristics are detailed in Table 1.

Safety and Tolerability

Two patients out of six with compensated (Child-Pugh A) cirrhosis discontinued treatment prematurely due to SAEs. Pulmonary arterial hypertension (PAH) was revealed by severe dyspnoea at treatment Week 6 in a patient (Fibroscan value: 42 kPa, Child-Pugh score: A5, platelet count: $58 \times 10^3/\mu L$) previously treated with four different antiviral regimens. Liver tests and renal function were normal. Mean pulmonary arterial pressure was 54 mmHg (right-heart catheterization). Symptoms improved after DAA discontinuation and treatment of PAH with bosentan and sildenafil [13].

Acute-on-chronic liver failure, ascribed to mitochondrial toxicity, occurred in a patient (Fibroscan value: 34 kPa, Child-Pugh score: A6, platelet count: $67 \times 10^3/\mu L$) with a history of oesophageal variceal bleeding 6 years before retreatment, without acute decompensation. The patient had no comorbidity. He had been previously treated with three different antiviral regimens. Jaundice developed at treatment Week 4 in the absence

of other symptoms. A further increase in serum conjugated bilirubin (up to 169 µmol/L) associated with pruritus and asthenia led to treatment discontinuation and hospitalisation. Within a few days alanine aminotransferase (ALT) increased moderately and prothrombin time (PT) decreased to subnormal levels. The clinical course was characterised by the development of ascites, Grade 1 renal failure and acute pancreatitis. There was a parallel steady increase in serum conjugated bilirubin level, associated with mild elevation of ALT levels (1.5 x upper limit of normal [ULN]) and PT remained subnormal. Markers of mitochondrial toxicity were transiently detectable, including elevation of creatine phosphokinase activity (3 x ULN) and blood lactates (4 mmol/L). The patient subsequently developed Grade 2 acute-on-chronic liver failure, with acute renal failure unresponsive to terlipressin, followed by spontaneous bacterial peritonitis 2 weeks after treatment discontinuation and severe sepsis with fatal outcome.

Efficacy

All patients achieved on-treatment virological response (HCV RNA <12 IU/mL), with SVR12 achieved by six patients (Table 2). Those failing to achieve SVR12 included two patients, both with HCV genotype 1a and cirrhosis, who relapsed post-treatment, and the two patients with SAEs.

The resistance profiles at retreatment baseline and after treatment in this study are detailed in Table 2.

DISCUSSION

In patients with HCV genotype 1 or 4, and F3 fibrosis or compensated cirrhosis, who have failed treatment with an NS5A inhibitor, EASL recommends retreatment with ribavirin plus sofosbuvir, grazoprevir and elbasvir or sofosbuvir, simeprevir and daclatasvir for 24 weeks [1]. Sofosbuvir, simeprevir and daclatasvir were the only HCV DAAs available as single agents at the time of the study. Therefore, this combination with or without ribavirin has been widely used off-label to retreat patients with advanced fibrosis or cirrhosis who failed to achieve SVR. Thus, we evaluated this combination in patients requiring retreatment.

Only the IMPACT study has evaluated a ribavirin-free version of the same regimen administered for 12 weeks in 40 treatment-naïve or treatment-experienced patients with decompensated cirrhosis or portal hypertension. No discontinuation due to adverse events occurred and a 100% SVR12 rate was achieved compared with a 60% SVR12 rate and discontinuation by two patients due to SAEs in our study [14]. The between-study differences can likely be explained by the fact that our patients had more advanced liver disease and had already failed a DAA-based regimen.

Both patients with SAEs discontinuing in our study had advanced liver disease, low platelet counts, and portal hypertension. However, neither had prior history of decompensation and they did not have an indication for liver transplantation. There have been reports of severe PAH in patients receiving interferon therapy [15], and in patients receiving sofosbuvir-containing therapy, suggesting that this SAE could be related to either their current or past treatment [13, 16].

In contrast, mitochondrial toxicity has not been reported with DAAs, although asymptomatic increases in lipase activity, lactic acidosis and two cases of self-limited

pancreatitis have been reported with sofosbuvir and simeprevir, and with sofosbuvir and ribavirin [17–20], indicating that the severe episode of mitochondrial toxicity observed in our study could be treatment related. Additionally, although the condition was diagnosed as mitochondrial toxicity at the time, we could not rule out protease inhibitor-induced hepatotoxicity.

The two patients who relapsed were infected with HCV genotype 1a, had cirrhosis (Fibroscan values: 15 and 22 kPa, respectively), and harboured NS5A and/or NS3 protease RASs at baseline known to confer reduced susceptibility to daclatasvir and simeprevir, respectively [10, 21–29]. As expected, NS5A and NS3 protease RASs were present after therapy in both patients. However, EASL does not recommend routine resistance testing prior to first-line treatment initiation due to unreliable access and no consensus on techniques. However, resistance testing is useful in patients exposed to NS5A inhibitors [1]. Therefore, clinicians should assess the likelihood of treatment failure based on other risk factors, e.g. advanced liver disease (irrespective of the HCV genotype or treatment regimen), HCV genotype 1, cirrhosis and low platelet count (suggestive of advanced liver disease with portal hypertension) [5, 10]. These two patients represent a particularly difficult-to-retreat subpopulation and emphasize the need for optimising first-line treatment of HCV, as recently recommended, in order to minimise treatment failure, selection of resistant viruses, and the subsequent need for rescue therapy [8].

This study is the first report on the safety and efficacy of retreatment with sofosbuvir, daclatasvir, simeprevir, and ribavirin for 24 weeks in HCV-infected patients. In conclusion, this open-label, “real-life” study indicates that this combination is initially efficacious in a heterogeneous population with compensated liver disease who failed prior

DAA treatment. However, relapses and SAEs had a major impact on the SVR rate. Thus, we suggest that this combination be used with extreme caution in patients with compensated cirrhosis. Other options should be available in the future for retreatment of patients who failed DAA-containing regimens.

Conflicts of Interest: Christophe Hézode has acted as a speaker and/or advisor for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals and Merck. Slim Fourati has acted as a speaker for Abbvie and Gilead Sciences. Stéphane Chevaliez has received research funding from the French Ministry of Health and the National Agency for Research on AIDS and Viral Hepatitis. He acted as an advisor to Abbott Diagnostics, Gilead Sciences, Janssen Pharmaceuticals and Merck. Françoise Roudot-Thoraval has acted as a speaker and/or advisor for Abbvie, Bristol-Myers Squibb, Gilead Sciences and Janssen Pharmaceuticals. Jean-Michel Pawlotsky has received research funding from Gilead Sciences. He has acted as an advisor for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals and Merck. The other authors have no conflicts of interest to declare.

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Table 1. Demographics and Baseline Characteristics

Parameter	Patients (N = 10)
Male, n (%)	7 (70)
Mean age, years (mean ± SD)	53.8 ± 7.2
BMI, kg/m^2 (mean ± SD)	27.4 ± 6.0
HCV genotype, n (%)	
1a	3 (30)
1b	2 (30)
1 undetermined	1 (10)
2a	1 (10)
4	2 (20)
6q	1 (10)
Median HCV RNA (range)	
× 10^6 IU/mL	1.22 (0.06–7.85)
Log$_{10}$ IU/mL	6.1 (4.78–6.89)
HCV RNA > 0.8 × 10^6 IU/mL, n (%)	7 (70)
Median Fibroscan value, kPa (range)	13.8 (7.5–42.3)
Stage of fibrosis	
Moderate fibrosis (Fibroscan > 7.0 to ≤ 9.5 kPa), n (%)	2 (20)
Severe fibrosis (Fibroscan > 9.5 to ≤ 12.5 kPa), n (%)	2 (20)
Compensated cirrhosis (Fibroscan > 12.5 kPa), n (%)	6 (60)
Child-Pugh score in patients with cirrhosis, n	
A5	4

A6	2
MELD score in patients with cirrhosis, mean (SD)	8.3 (1.8)
Prior DAA-containing treatment	
Sofosbuvir plus daclatasvir, n (%)	5 (50)
Sofosbuvir plus simeprevir, n (%)	2 (20)
Sofosbuvir/ledipasvir, n (%)	1 (10)
Grazoprevir/elbasvir, n (%)	1 (10)
Mericitabine plus danoprevir, n (%)	1 (10)
Patients with ≥ 1 NS3 protease RAS at baseline, n (%)	5 (50)
Patients with ≥ 1 NS5A RAS or deletion at baseline, n (%)	7 (70)
Patients with ≥ 1 NS5B RAS at baseline, n (%)	3 (30)
Mean creatinine, µmol/L (mean ± SD)	74.4 ± 13.1
Mean albumin, g/L (mean ± SD)	39.6 ± 3.0
Mean hemoglobin, g/dL (mean ± SD)	15.3 ± 1.3
Mean platelet count, × 10^3/µL (mean ± SD)	155 ± 75
Mean prothrombin INR (mean ± SD)	1.1 ± 0.1
Mean total bilirubin, µmol/L (mean ± SD)	15.7 ± 9.0

Abbreviations: BMI, body mass index; DAA, direct-acting antiviral; HCV, hepatitis C virus; INR, international normalised ratio; MELD, model for end-stage liver disease; RAS, resistance-associated substitution; SD, standard deviation.

Table 2. Virological Outcomes According to the Presence of HCV Resistance-Associated Substitutions (RASs) at Baseline, and RASs at Relapse in Patients Treated with Sofosbuvir, Daclatasvir and Simeprevir with Ribavirin for 24 weeks

HCV genotype	Prior regimen	Cirrhosis (Child-Pugh)	RASs at baseline NS3/4A	NS5A	NS5B	Last on-treatment HCV RNA, IU/mL	SVR12	RASs at relapse in patients not achieving SVR12 NS3/4A	NS5A	NS5B
1a	Sofosbuvir Simeprevir	Yes (A5)	R155K, D168E	M28A, Q30K	None	< 12 (EOT)	Relapse	R155K, D168E	M28A, Q30K	None
1a	Sofosbuvir Daclatasvir	Yes (A5)	None	M28T	None	< 12 (EOT)	Relapse	R155K	Q30E	None
1a	Sofosbuvir Daclatasvir	Yes (A5)	R155K	Q30K	None	< 12 (Week 4)	Discontinued*	R155K	M28T, Q30K	None
1[†]	Sofosbuvir Daclatasvir	Yes (A6)	None	L28I	None	< 12 (Week 6)	Discontinued (death)[‡]	_[§]	_[§]	_[§]
1b	Danoprevir Mericitabine	No	S122N	P58S, Y93H	S556G	< 12 (EOT)	Yes	–	–	–
1b	Sofosbuvir Ledipasvir	Yes (A6)	None	None	C316N	< 12 (EOT)	Yes	–	–	–
2a	Sofosbuvir Daclatasvir	Yes (A5)	None	None	None	< 12 (EOT)	Yes	–	–	–
4h	Sofosbuvir Simeprevir	No	D168E	L28M	L159F	< 12 (EOT)	Yes	–	–	–

4a	Sofosbuvir Daclatasvir	No	None	L30S, Y93H	None	< 12 (Week 12)	Yes	–	–	–
6q	Grazoprevir Elbasvir	No	V36I, Y56H, D168C	None	None	< 12 (EOT)	Yes	–	–	–

*Discontinued treatment due to a SAE (pulmonary hypertension; for details see Safety and Tolerability section, and Savale et al, 2016 [14]).

[†]The HCV subtype was determined by phylogenetic analysis with bootstrapping of a portion of the NS5B coding region.

[‡]Treatment discontinued due to a SAE (mitochondrial toxicity, multi-organ failure and death; for details see Safety and Tolerability section).

[§]No relapse at the time of death, 3 weeks after early treatment discontinuation.

Abbreviations: EOT, end of treatment; HCV, hepatitis C virus; RAS, resistance-associated substitution; SVR12, sustained virological response (HCV RNA < 12 IU/mL) at 12 weeks post treatment.