Observational Study

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Effectiveness and safety of simeprevir-based regimens for hepatitis C in Italy

The STIly observational study

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Abstract

The combination of the direct-acting antivirals, simeprevir (SMV) and sofosbuvir (SOF), was the first highly efficacious interferon-free combination for treating patients with hepatitis C virus (HCV), and was widely used in Italy as a result.

The aim of this study was to evaluate effectiveness and safety of SMV in Italian patients with HCV genotype (GT) 1 and 4 overall, by treatment regimen [SMV/SOF and SMV/SOF+ribavirin (RBV)], cirrhosis status, and GT (GT1a, GT1b, and GT4).

An observational multicenter cohort study was conducted in 46 centers across Italy. Adult HCV + GT1 or GT4 patients, naive or treatment-experienced, with or without cirrhosis, who underwent treatment with a SMV-containing regimen from May to September 2015 were included. The primary endpoint was sustained virologic response (SVR), defined as undetectable serum HCV RNA levels 12 weeks after treatment end (SVR12). The secondary endpoints included duration of treatment, safety and tolerability of each treatment regimen, and SVR by treatment and according to response to previous treatment and fibrosis stage. The association between SVR and a subset of the most clinically relevant variables was investigated by a multivariate logistic regression analysis.

A total of 349 HCV-positive patients treated with an SMV-based regimen were enrolled, of whom 342 received SMV/SOF ± RBV and were included in this analysis. Most patients (59.4%) were treatment-experienced and had cirrhosis (78.1%). In the group receiving SMV/SOF + RBV, most (63.1%) were treatment-experienced and 82.9% had cirrhosis. Three patients were lost to follow-up; 330 patients receiving SMV/SOF ± RBV (96.5%) were treated for 12 weeks. Overall, SVR12 was achieved by 324 patients [94.2%, 95% confidence interval (95% CI) 92–97]. When stratified by treatment and clinical and virologic characteristics, SVR12 was achieved by 77 of 79 [97.5% (95% CI 94.0–100.0)] and 247 of 263 [93.9% (95% CI 91.0–96.8)] patients receiving SMV/SOF and SMV/SOF + RBV, respectively; 132 of 139 (95.0%) naive versus 192/203 (94.6%) treatment-experienced patients; 250 of 267 (93.6%) cirrhotic and 56 of 62 (90.3%) HIV coinfected patients. SMV-based regimens were generally well tolerated. Adverse events leading to treatment discontinuations were not observed.

A high proportion of patients treated with SMV/SOF-based regimens achieved SVR12 in this study. A high SVR12 rate was also achieved in patients with cirrhosis, treatment experience, and HUV coinfected patients.

Abbreviations: AE = adverse event, BMI = body mass index, CI = confidence interval, DAA = direct-acting antivirals, eGFR = estimated glomerular filtration rate, EOT = end of treatment, GT = genotype, HCV = hepatitis C virus, IFN = interferon, mITT = modified intention-to-treat, OR = odds ratio, RBV = ribavirin, SAE = serious adverse event, SD = standard deviation, SMV =

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simeprevir, SOF = sofosbuvir, SVR = sustained virologic response, SVR12 = undetectable serum HCV RNA levels 12 weeks after treatment end, VBT = virologic breakthrough.

Keywords: cirrhosis, hepatitis C, real-world evidence, simeprevir, sofosbuvir

1. Introduction

In the last 2 decades, the management of patients with hepatitis C virus (HCV) infection has substantially changed thanks to a better understanding of the pathophysiology, the development of diagnostic procedures, and an improvement in the therapy.

In particular, the approval of the direct-acting antivirals (DAAs) simeprevir (SMV, an NS3/4A protease inhibitor) and sofosbuvir (SOF, a first-in-class NS5B replication complex inhibitor) led to the use of the first available interferon (IFN)-free regimen for genotypes (GT) 1 and 4, and a reduction in treatment duration.[1,2] The combination SMV/SOF, with or without ribavirin (RBV), was approved on the basis of the results of the COSMOS study in which more than 90% of patients with HCV GT1 naive and null responder achieved a sustained virologic response at Week 12 (SVR12).[3] These results were confirmed by SVR rates of 97% in the OPTIMIST-1 trial[4] in HCV GT1 patients without cirrhosis, while SVR rates of 83% were observed in the OPTIMIST-2 trial in patients with cirrhosis.[5]

Following this first very active and widely used IFN-free combination, other DAAs became available for treating HCV-positive patients with all genotypes. The availability of DAAs has allowed a wide range of patients to be cured, leading to an SVR rate above 90%.

STIly is an observational multicenter cohort study originally designed to evaluate effectiveness and safety of a telaprevir-based regimen in patients with HCV GT1. Here, we present the expansion of the STIly study, which includes both HCV GT1 and GT4 patients treated with SMV-based regimens (SMV/SOF and SMV/SOF + RBV). This paper focuses on effectiveness and safety of SMV in Italian patients infected with HCV GT1 and GT4 overall, by treatment regimen, cirrhosis status, and genotype (GT1a, GT1b, and GT4).

2. Materials and methods

2.1. Study design and setting

STIly is an observational multicenter cohort (prospective and/or retrospective) study in HCV-infected patients treated with a telaprevir- or SMV-based regimen, conducted in the routine clinical setting. Following the authorization of the new therapeutic option, the original STIly study protocol was amended to include patients treated with a SMV-based regimen. The primary objective of the amended study was to evaluate the SVR, according to prior treatment history and fibrosis stage, in a cohort of Italian patients with HCV who followed a SMV-based regimen in clinical practice. Main secondary objectives included the evaluation of SVR by treatment regimen, treatment history (naive, relapser, partial responder, null responder, or unknown responder), and fibrosis stage, and the description of the safety profile. The sample size was determined on the basis of feasibility criteria according to the number of patients managed by the centers in their practice.

This study involved 46 centers across Italy and enrolled a total of 552 patients from May 2014 to September 2015. The initial protocol was amended to redefine the observed population, in order to include and describe patients after they were treated consecutively with SMV-based regimens, and to update and increase the information collected on the wider population. In the amended study, 349 patients who had completed a SMV-based regimen were consecutively enrolled from May 2015 to September 2015. These patients were identified retrospectively after the end of SMV treatment, but were followed-up prospectively for 12 or 24 weeks after treatment. The maximum period of prospective observation was 24 weeks, while the maximum period of retrospective observation was 48 weeks, that is, up to 24 weeks of SMV IFN-free regimen and up to 24 weeks after the end of therapy. Effectiveness and tolerability data were collected retrospectively for the entire duration of SMV treatment, and retrospectively and/or prospectively for up 12 (or 24) weeks after the end of the therapy (SVR12 or SVR24). The duration of SMV treatment was determined by the treating physician, in accordance with the product label.

Data were extracted exclusively from clinical charts and were collected using an electronic case report form. The original and amended protocols, and the informed consent, were approved by the local ethics committees of all participating centers.

2.2. Participants

Adult patients (aged ≥18 years) with evidence of HCV GT1 or GT4 infection who had received a SMV regimen (IFN-free or -based) and who had a quantifiable plasma HCV RNA before treatment start were eligible for inclusion in this observational study. Eligible patients could have been treatment-naive or treatment-experienced before the start of SMV-based therapy with or without cirrhosis. Patients with any grade of cirrhosis were eligible for inclusion in the study; the study predated the label change for SMV, recommending against its use in patients with Child–Pugh Stage B or C hepatic dysfunction.[1]

All patients provided written informed consent before collection of any data. Patients were excluded from the study if any of the following criteria was present: infection or coinfection with an HCV genotype other than GT1 or GT4; previous use of investigational HCV protease or polymerase inhibitors; participation in any concomitant clinical trial with SMV and any condition that, in the opinion of the investigator, would compromise the well-being of the patients or the participation in the study. The enrollment in a clinical trial with SMV, the withdrawal of informed consent, and death were causes of premature study discontinuation, while treatment discontinuation was not a reason for withdrawal. Patients were stratified by prior treatment history, fibrosis, and HCV genotype.

2.3. Study endpoints and study assessments

The primary endpoint of the study was the SVR, defined as undetectable serum HCV RNA levels at Week 12 after treatment end (SVR12). The secondary endpoints included the duration of treatment, safety and tolerability of each treatment regimen, and SVR by treatment regimen and according to response to previous treatment and fibrosis stage.

Start date (baseline) was the date of first SMV administration; treatment end date was the last administration of SMV/SOF ± RBV. Baseline information on patient demographic characteristics, clinically relevant concomitant diseases, genotype, fibrosis

stage, previous HCV therapy and response, serum HCV RNA levels, and other concomitant therapies were retrospectively collected from patient records. During their treatment, HCV RNA was assessed at Week 4 and at the end of treatment (EOT 12 or 24 weeks) and in the follow-up visits at Week 12 (or 24 if SVR12 was not available) after EOT. Some of these data were collected prospectively and some retrospectively, depending on when the patient entered the study. The HCV RNA levels were measured by investigators in each center as per clinical practice, the response to previous treatment (naive or experienced) was evaluated according to data from the patient's clinical charts, and the fibrosis stage was evaluated before treatment start by means of liver assessment (Fibroscan, biopsy, or echography results). Safety profile was described in terms of adverse events (AEs) and serious adverse events (SAEs) that occurred both during the therapy and/or during the follow-up. Each AE was reported in terms of description, duration, severity, outcome, and correlation with study drug.

2.4. Statistical analyses

Baseline of the study was the start date of the retrospective observation period and follow-up was calculated from this date to the last study visit. All patients who met the study inclusion criteria and received at least 1 dose of SMV, and had SVR data available [modified intention-to-treat (mITT) population], were included in the statistical analysis. The description of baseline sociodemographic and clinical variables varied for quantitative and qualitative variables. Quantitative variables were described by mean, standard deviation, median, first and third percentile, minimum, and maximum. Qualitative variables were described by absolute and relative frequency. Bilateral 95% confidence intervals (95% CIs) were calculated where relevant.

The proportion of patients with SVR was calculated as the total number of patients with SVR/total number of evaluable patients. The SVR was computed overall and separately within the subgroups defined by response to previous treatment (naive or experienced), fibrosis stage (cirrhosis, noncirrhosis), and HIV coinfection status. SVR12 evaluable patients had available HCV RNA levels at the EOT and at Week 12±4 weeks after treatment end.

Patients who discontinued SMV for any reason (AEs, detectable HCV RNA at Week 4 or 12 of treatment, lost to follow-up, withdrew informed consent, other reasons) were considered evaluable for analyses if they met the inclusion or exclusion criteria, received at least 1 dose of SMV, and had evaluable SVR data. Patients who failed to meet the inclusion or exclusion criteria, or without at least one dose of SMV or without evaluable SVR, were excluded from the analysis. Patients with missing data values were not excluded from the analysis, their data were not replaced; frequency of missing data was given for all analyzed data sets.

The safety profile was evaluated retrospectively or prospectively in terms of patients with at least 1 AE or SAE, and as total number of recorded AEs and SAEs overall and by treatment group. AEs and SAEs were also described in terms of clinical presentation, causality, and action taken.

2.5. Sensitivity analysis

Different logistic regression analyses were performed in order to assess which baseline variables were associated with SVR12. The response variable was presence/absence of SVR, while the following parameters were considered as covariates: fibrosis stage (cirrhosis or noncirrhosis), response to previous treatment (naive or experienced), age, gender, albumin level, platelet count, HIV coinfection, treatment with RBV, body mass index (BMI), and HCV genotype. Furthermore, a multivariate logistic regression analysis was performed on a subset of the most clinically relevant variables, in order to explore their association with SVR. The odds ratio (OR) estimates provided by the model evaluated the association between SVR and the variables included in the analysis.

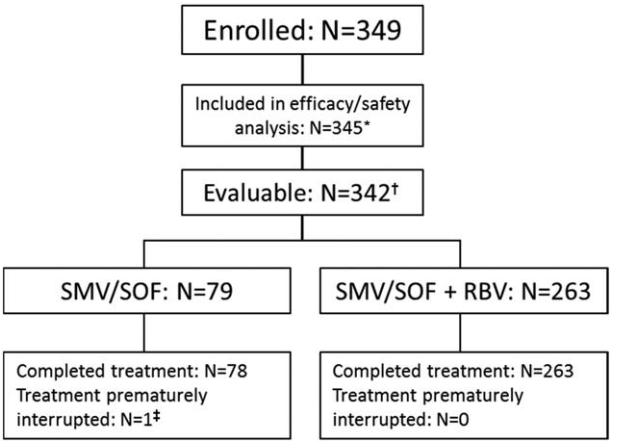

Figure 1. Patients flow. *Four patients were excluded from the analysis because they had SMV/peginterferon+RBV (N=3) or SMV/daclatasvir+RBV (N=). †Three patients were excluded from the analysis because SVR12 could not be assessed. In particular, they were followed-up during treatment administration, but they were lost to follow-up and did not show up again. Two of three patients had last viral load 1 day after treatment end and it was undetectable, 1 patient 4 weeks after treatment end (HCV RNA was undetectable). ‡Treatment was discontinued after 49 days because of a SAE (progressive increase of pancreatic cytolytic parameters). Follow-up was continued and the patient achieved SVR12.

3. Results

A total of 349 patients were enrolled in 46 Italian centers from May to September 2015. Out of 349 patients selected for treatment with a SMV-based regimen, 345 received SMV/SOF± RBV and were included in the present efficacy and safety analysis, and 342 were included in the mITT population. Seven were excluded from the analysis because they received nonstudy regimens (n=4) or SVR could not be assessed (n=3). The flow of patients into the study and number of patients in the analyzed groups are reported in Fig. 1.

3.1. Patients baseline characteristics

The demographic, clinical, and virologic characteristics of patients at baseline are reported in Table 1. The patients were mainly men (67%) and had a mean (standard deviation) age of 58.7 (10.4) years. Overall, 267 patients (78.1%) were cirrhotic (49 in the SMV/SOF group and 218 in the SMV/SOF+RBV group) and 62 (18.1%) were coinfected with HIV (14 in the SMV/SOF group and 48 in the SMV/SOF+RBV group). Two hundred three patients (59.4%) were treatment-experienced and 281 patients (82.2%) were infected with HCV GT1, of whom 92 (26.9%) and 189 (55.3%) were GT1a and GT1b, respectively. The group of patients who received RBV in addition to SMV/SOF included a high proportion of treatment-experienced patients and those with cirrhosis.

Table 1

Baseline patient demographic, clinical, and virologic characteristics.

	SMV/SOF N = 79	SMV/SOF + RBV N = 263	All N = 342
Demographics			
Male, n (%)	44 (55.7)	185 (70.3)	229 (67.0)
Age, y			
Mean (SD)	58.6 (10.3)	58.7 (10.0)	58.7 (10.1)
≥70 y	14.0 (17.7)	42.0 (16.0)	56 (16.4)
BMI, n (%)			
<18.5 (underweight)	3 (3.8)	2 (0.8)	5 (1.5)
18.5–25 (normal)	38 (48.1)	125 (47.5)	163 (47.7)
25–30 (overweight)	24 (30.4)	93 (35.4)	117 (34.2)
≥30 (obese)	8 (10.1)	32 (12.2)	40 (11.7)
Not calculated	6 (7.6)	11 (4.2)	17 (5.0)
Clinical characteristics			
Prior therapy, n (%)			
Naive	42 (53.2)	97 (36.9)	139 (40.6)
Treatment-experienced	37 (46.8)	166 (63.1)	203 (59.4)
HCV genotype, n (%)			
1a	22 (27.8)	70 (26.6)	92 (26.9)
1b	46 (58.2)	143 (54.4)	189 (55.3)
4	11 (13.9)	50 (19.0)	61 (17.8)
HCV RNA (log_{10})			
Mean (SD)	6.4 (6.4)	6.3 (6.4)	6.3 (6.4)
Median	6.2	6.1	6.1
Fibroscan value, n (%)			
Available at therapy start	56 (70.9)	201 (76.4)	257 (75.1)
≥25 kPa	14 (25.0)	53 (26.4)	67 (26.1)
13–25 kPa	18 (32.1)	102 (50.7)	120 (46.7)
<13 kPa	24 (42.9)	46 (22.9)	70 (27.2)
Cirrhosis, n (%)*	49 (62.0)	218 (82.9)	267 (78.1)
Comorbidity, n (%)			
Arterial hypertension	25 (31.6)	75 (28.5)	100 (29.2)
HIV	14 (17.7)	48 (18.3)	62 (18.1)
Diabetes	9 (11.4)	45 (17.1)	54 (15.8)
Metabolic syndrome	3 (3.8)	15 (5.7)	18 (5.3)
Liver transplant, n (%)	3 (3.8)	8 (3.0)	11 (3.2)
eGFR value, n (%)†			
Available at therapy start	74 (93.7)	251 (95.4)	325 (95.0)
<70 mL/min/1.32 m^2	12 (16.2)	25 (10.0)	37 (11.4)
Creatinine value, n (%)†			
Available at therapy start	74 (93.7)	251 (95.4)	325 (95.0)
<1 mg/dL	61 (82.4)	206 (82.1)	267 (82.2)
Platelets, n (%)†			
Available at therapy start	71 (89.9)	252 (95.8)	323 (94.4)
<100 x 10^3/mmc	21 (29.6)	90 (36.1)	111 (34.4)
≥100 x 10^3/mmc	50 (70.4)	162 (64.3)	212 (65.6)
Albumin, n (%)†			
Available at therapy start	65 (82.2)	240 (91.2)	305 (94.4)
<3.5 g/dL	11 (16.9)	30 (12.5)	41 (13.4)
≥3.5 g/dL	54 (83.1)	210 (87.5)	264 (86.6)
SMV-based therapy			
Treatment duration, n (%), wks			
<12	1 (1.3)	0	1 (0.3)
12	76 (96.2)	254 (96.6)	330 (96.5)
>12 and <24	1 (1.3)	1 (0.4)	2 (0.6)
24	1 (1.3)	7 (2.7)	8 (2.3)
>24	0	1 (0.4)	1 (0.3)

* Cirrhosis diagnosed on the basis of Fibroscan, biopsy, or echography results.

† Percentages were calculated from the total number patients at therapy start.

3.2. Virologic response

Overall SVR12 was achieved by 324 patients (94.7%; 95% CI 92–97). As reported in Table 2, SVR12 was experienced in 77 of 79 (97.5%; 95% CI 94-100) and 247 of 263 (93.9%; 95% CI 91-97) patients receiving SMV/SOF and SMV/SOF + R, respectively.

When stratified by clinical and virologic characteristics, SVR12 was achieved by 132 of 139 (95.0%) naive patients versus 192 of 203 (94.6%) treatment-experienced patients. Furthermore, 250 of 267 (93.6%) cirrhotic patients and 56 of 62 (90.3%) patients with HIV achieved SVR12. Figure 2 reports

Table 2

Sustained virologic response, 12 weeks after end of treatment.

	SMV/SOF (N = 79)	SMV/SOF + RBV (N = 263)	All (N = 342)
SVR12			
N (%)	77 (97.5)	247 (93.9)	324 (94.7)
95% CI	94–100	91–97	92–97

SVR12 stratified by prior treatment history, fibrosis, and genotype.

Among nonresponder patients, 1 patient (0.3%) had a virologic breakthrough (VBT), 17 (5.0%) patients relapsed after SMV/SOF ± RBV therapy, and 1 patient in the SMV/SOF + RBV group was a nonresponder to treatment. The patient with VBT had received SMV/SOF + RBV and was male, HCV GT1a, treatment-naive, and cirrhotic. Details on the relapsed patients are provided by treatment regimen in Table 3.

3.3. Sensitivity analysis

Univariate and multivariate logistic regression analyses were conducted to identify factors associated with SVR12 rates. The univariate logistic regression did not identify any factors significantly associated with SVR12.

Therefore, a sensitivity analysis was performed in order to verify the results, including age, BMI, Fibroscan, platelets, and albumin. Again, no parameter was significantly associated with SVR12 in the univariate logistic regression.

However, in these regression analyses, the OR associated with baseline platelet levels was close to the margin of statistical significance, so another multivariate model was calculated. This model excluded albumin (<3.5 vs ≥3.5 g/dL) because this parameter had a low association with SVR in the previous analyses and information on albumin was available for only 10% of patients. The model also excluded fibrosis stage (cirrhosis vs noncirrhosis) because this parameter was strongly associated with platelet levels ($P < .001$), and including both these variables at the same time could affect the model's goodness of fit and lead to wider CIs.

The results of the new model (Fig. 3) show that the probability of achieving SVR12 was significantly lower (OR = 0.343; 95% CI 0.126–0.931) when platelets were <100 x 1000/mmc versus ≥100 x 1000/mmc.

Table 3

Clinical characteristics of relapsed patients.

Patient characteristics	Relapsed patients, N (%)		
	SMV/SOF (N = 2)	SMV/SOF + RBV (N = 15)	All (N = 17)
Male	2 (100)	12 (80)	14 (82.4)
≥70 y	1 (50)	1 (6.7)	2 (11.8)
Naive	0 (0)	6 (40.0)	6 (35.3)
Experienced	2 (100)	9 (60.0)	11 (64.7)
Cirrhosis	2 (100)	14 (93.3)	16 (94.1)
Genotype			
1a	1 (50)	6 (40.0)	7 (41.2)
1b	1 (50)	5 (33.3)	6 (35.3)
4	0 (0)	4 (26.7)	4 (23.5)
HIV coinfection	0 (0)	6 (40.0)	6 (35.3)

In light of these results, univariate and multivariate analyses were performed in the subgroup of patients with platelets <100 x 1000/mmc (n = 111). The univariate analysis identified a potential inverse association of SVR12 with GT1a or HIV coinfection (Fig. 4). The probability of achieving SVR12 was lower in patients with HCV GT1a versus patients with HCV GT1b (OR = 0.138; 95% CI 0.026–0.727) and in patients with HIV coinfection versus monoinfected patients (OR = 0.188; 95% CI 0.049–0.726). However, the multivariate analysis did not confirm these associations (Fig. 5).

3.4. Safety profile

Safety data were available from 342 patients. SMV/SOF ± RBV was well tolerated, with 33.6% and 1.2% of patients having at last 1 AE or SAE reported, respectively (Table 4). Overall, 218 AEs were reported in 115 patients; of these, 35 AEs occurred in 23 patients (39%) receiving SMV/SOF and 183 occurred in 92 (35%) patients receiving SMV/SOF + RBV. One hundred seven of 218 AEs (49%) were considered related to RBV, while 105 of 218 (48%) and 53 of 218 (25%) AEs were considered related to SMV and SOF, respectively. RBV dose was reduced due to 34 AEs and interrupted following 6 AEs; in 1 case, SMV and SOF were

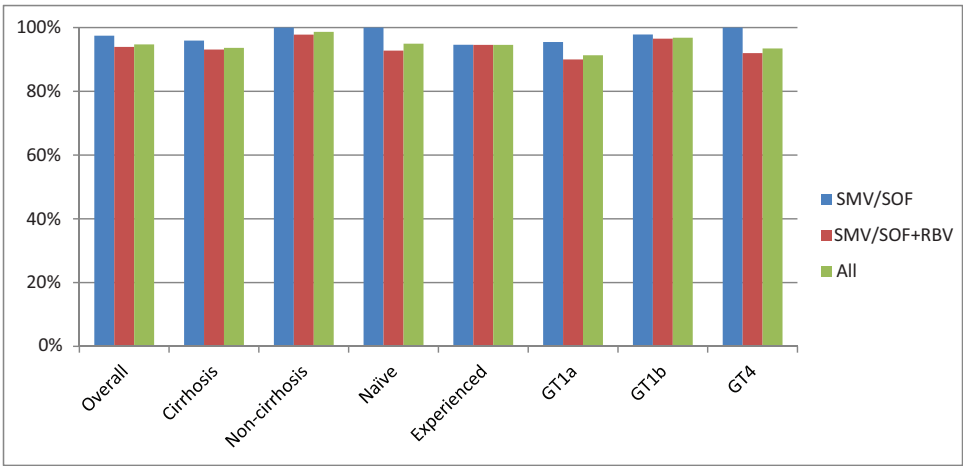

Figure 2. SVR12 in subgroups stratified by prior treatment history, cirrhosis, and genotype.

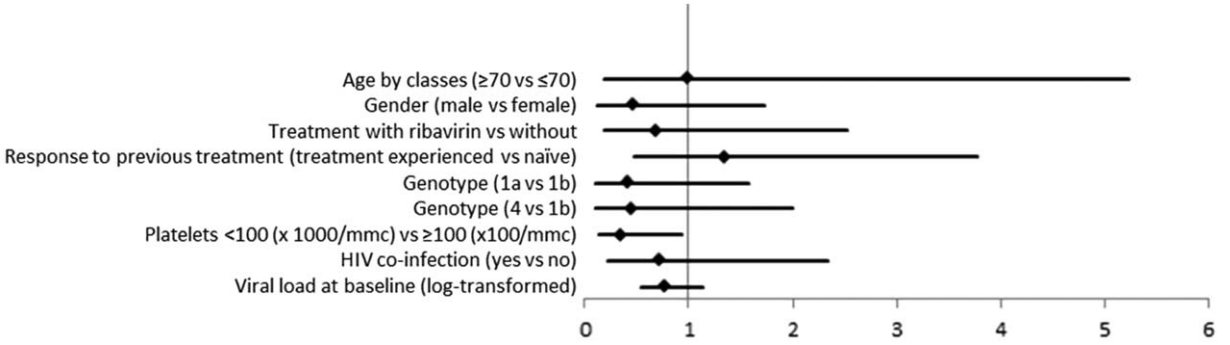

Figure 3. Multivariate logistic regression.

withdrawn due to AEs. SAEs occurred in 1 (1.3%) and 3 (1.1%) patients receiving SMV/SOF and SMV/SOF + RBV, respectively. All SAEs were of moderate severity, required hospitalization, and resolved. Specifically, pneumonia occurred in a 53-year-old female patient who was infected with HCV GT1a and HIV, was naive to treatment, had cirrhosis, and was receiving SMV/SOF + RBV (SAE was not considered to be related to treatment). One 58-year-old male patient who was infected with HCV GT1b, was treatment-experienced, and had cirrhosis experienced erysipelas; this AE was considered to be doubtfully related to SMV and RBV. Hyponatremia was experienced by a 76-year-old male patient who was infected with HCV GT1b, was treatment-experienced, had cirrhosis, and was receiving SMV/SOF + RBV. Hyponatremia was doubtfully related to treatment and RBV was interrupted. One 65-year-old male patient infected with GT1b who was naive to treatment and had bridging fibrosis developed a progressive increase in pancreatic cytolytic parameters during treatment with SMV/SOF. The patient was hospitalized, had SMV and SOF discontinued, and the SAE resolved. Investigators considered that this SAE was very likely related to SMV and probably related to SOF.

4. Discussion

The landscape of treatment for HCV infection has evolved rapidly since the introduction of highly effective HCV DAA therapies. The first IFN-free combination of DAAs available was SMV + SOF ± RBV.

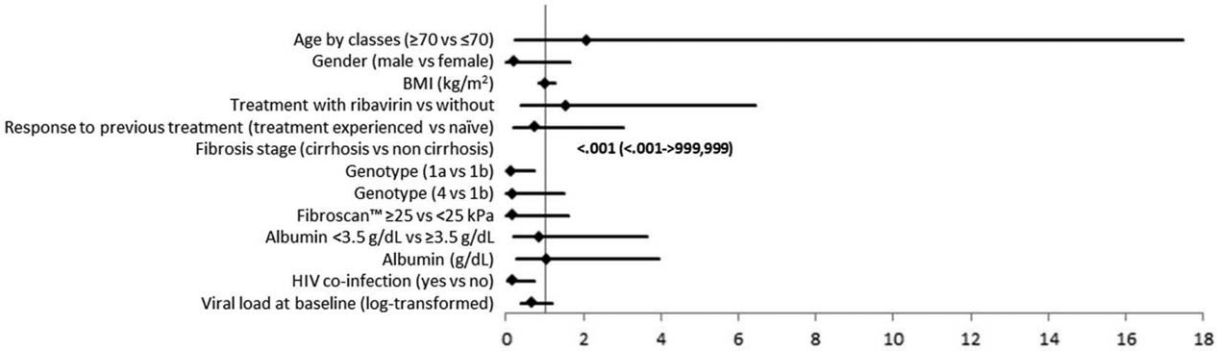

Figure 4. Univariate analysis in the subgroup of patients with platelets <100 x 1000/mmc (N = 111).

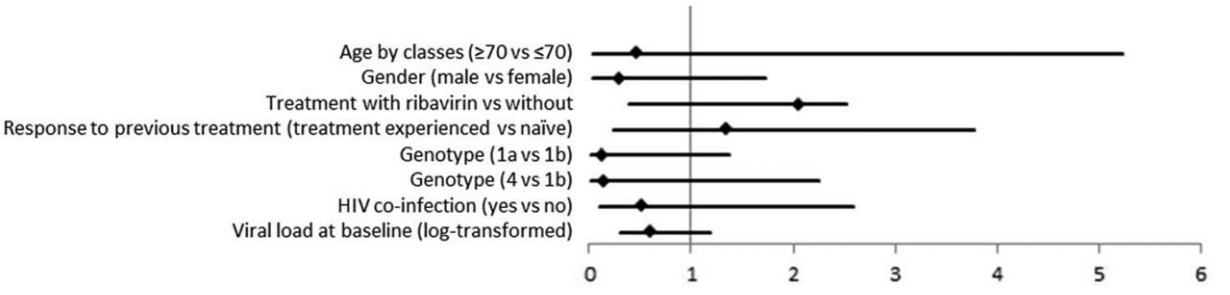

Figure 5. Multivariate analysis in the subgroups of patients with platelets <100 x 1000/mmc (N = 111).

Table 4

Safety profile of simeprevir-based regimen.

	SMV/SOF N = 79	SMV/SOF + RBV N = 263	Total N = 342
Patients with at least one AE, N (%)	23 (29.1)	92 (35.0)	115 (33.6)
Total occurred AEs, N	35	183	218
Most frequent AEs,* N (%)			
Asthenia	5 (6.3)	29 (11.0)	34 (9.9)
Anemia	2 (2.5)	31 (11.8)	33 (9.6)
Hyperbilirubinemia	1 (1.3)	27 (10.3)	28 (8.2)
Itching	4 (5.1)	9 (3.4)	13 (3.8)
Headache	4 (5.1)	7 (2.7)	11 (3.2)
Insomnia	1 (1.3)	6 (2.3)	7 (2.0)
Patients with at least 1 SAE, N (%)	1 (1.3)	3 (1.1)	4 (1.2)
Total occurred SAEs, N	1	3	4
Pneumonia	0 (0)	1 (33.3)	1 (25.0)
Erysipelas	0 (0)	1 (33.3)	1 (25.0)
Hyponatremia	0 (0)	1 (33.3)	1 (25.0)
Progressive increase of pancreatic cytolytic parameters†	1 (100.0)	0 (0)	1 (25.0)

* Incidence ≥2% (percentages are calculated over the total number of patients in the respective groups).

† The patient was hospitalized, had SMV and SOF discontinued, and the SAE resolved. Investigators considered that this SAE was very likely related to SMV and probably related to SOF.

In the STIly study, overall SVR12 was achieved by 324 (94.7%; 95% CI 92–97) patients, with very high cure rate observed with SMV/SOF without RBV (97.5%; 95% CI 94–100) and with RBV addition (93.9%; 95% CI 91–97), showing for the first time that DAAs without RBV can be highly effective in curing hepatitis C.

The population assessed in the STIly study included a majority of difficult-to-treat patients with cirrhosis (78.1%) and prior treatment experience (59.4%), and in general, patients presented a more advanced disease than those included in clinical trials. However, high SVR12 rates (≥90%) were seen regardless of fibrosis stage and prior treatment history. Furthermore, the SMV-based regimen was well tolerated and did not lead to AE-related treatment discontinuations. The safety profile of SMV used in combination with SOF ± RBV in patients with HCV with advanced liver disease is in line with that reported in SMV registration trials.[3–5]

Effectiveness results from the STIly study are consistent with those from other observational studies on both HCV GT1 and GT4.[6–13]

The STIly study showed an SVR12 rate of 90% in HIV-coinfected patients (n = 56/62). This rate was comparable to the SVR12 achieved in HCV-monoinfected patients (96%; n = 268/280). Furthermore, the safety data from the HIV-coinfected patients in the STIly study were comparable with those in the HCV-monoinfected patients, and in line with that reported in the SMV registration trial.

These results showed that SMV/SOF, the first commercially available DAA combination, is highly efficacious in a heterogeneous population of real-world patients, just as it was in the more carefully selected populations of patients who participated in the original phase 3 clinical registration trials results.

The limitations of this study were that the 2 DAA regimens (SMV/SOF and SMV/SOF + RBV) were not compared head-to-head and the choice of regimen was determined by the physicians according to patients' characteristics and their own preferences. Therefore, differences in SVR12 seen in the 2 groups of patients could be related to the severity of conditions rather than to the true effectiveness of the regimen. The lack of a statistically significant association between SVR12 and some variables (e.g., albumin, genotypes, and HIV coinfection) may be related to missing data affecting the power of analysis.

In conclusion, these DAA combinations have been the first to show effectiveness in a wide range of patients with HCV. These results cannot be compared with those achieved with subsequent IFN-free combinations, as they were obtained in very advanced patients, a high proportion of whom had cirrhosis (both compensated and decompensated) and comorbid conditions while waiting for the availability of IFN-free regimens.

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