International Journal of Infectious Diseases 62 (2017) 64–71

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

HCV mono-infected and HIV/HCV co-infected individuals treated with direct-acting antivirals: to what extent do they differ?

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ARTICLE INFO

Article history:
Received 28 February 2017
Received in revised form 3 July 2017
Accepted 4 July 2017
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Direct-acting antivirals
DAAs
SVR
Safety
HIV/HCV co-infection
Real world

ABSTRACT

Background: Direct-acting antiviral (DAA)-based treatment of hepatitis C virus (HCV) has been associated with high sustained virological response (SVR) rates and good tolerability in randomized clinical trials. This study was performed to assess the safety and effectiveness of DAAs in both HCV mono-infected and HIV/HCV co-infected patients.

Methods: All consecutive HCV-infected patients, including HIV/HCV co-infected patients, receiving DAA-based treatment from February 2015 to September 2016 at the study clinic were included. Clinical, virological, and biochemical data were retrieved. The primary end-point was the SVR12 (HCV RNA undetectable 12 weeks after the end of treatment) is commonly used worldwide. The secondary end-point was the safety profile of DAAs during the treatment period.

Results: A total of 382 patients were included; 62 were HIV/HCV co-infected. Cirrhosis was found in 256 patients (67.4%). SVR12 was achieved in 365/382 (95.5%) individuals (58/62 HIV/HCV co-infected, 93.5%) in the intention-to-treat (ITT) analysis. A platelet count $<90 \times 10^9$/l (odds ratio (OR) 4.12, 95% confidence interval (CI) 1.5–11.3, $p = 0.006$), HCV genotype 3 infection (OR 5.49, 95% CI 1.9–15.7, $p = 0.002$), liver stiffness >20 kPa (OR 3.05, 95% CI 1.03–8.96, $p = 0.04$), and Model for End-Stage Liver Disease (MELD) score >10 (OR 5.27, 95% CI 1.16–23.8, $p = 0.03$) were associated with lower SVR rates. On multivariate analysis, only genotype 3 infection remained a negative predictor of SVR (OR 21.6, 95% CI 3.81–123, $p = 0.001$). Treatment discontinuation was observed in 10 subjects. Severe adverse events (SAEs) occurred in 17 patients (4.5%).

Conclusions: High SVR12 rates were observed in both HCV mono-infected and HIV/HCV co-infected individuals. Overall, DAA-based treatment was safe and there were no differences in terms of SAEs and treatment discontinuation between the two groups.

Introduction

Globally, an estimated 130–170 million people are infected with the hepatitis C virus (HCV), and the virus is found in 10–30% of all people living with an HIV infection (Hajarizadeh et al., 2013; Wyles et al., 2016). Furthermore, chronic HCV infection is still a major cause of liver disease worldwide (Hajarizadeh et al., 2013). In addition, HCV-related liver disease has emerged as a leading non-HIV cause of death in HIV/HCV co-infected subjects as a result of an accelerated liver fibrosis process (Wyles et al., 2016).

For nearly two decades, interferon (IFN)-based treatment was the only therapeutic option against HCV infection. This treatment is characterized by very low sustained virological response (SVR) rates, particularly in HIV/HCV co-infected individuals (Wyles et al., 2016; Sulkowsky, 2016). The recent introduction of direct-acting antivirals (DAAs) has widely changed the anti-HCV treatment scenario, improving SVR rates and promising a dramatic reduction in HCV-related morbidity and mortality (Flisiak et al., 2017; EASL Recommendations on Treatment of Hepatitis C, 2016). Moreover, the favourable safety profile of DAAs reported in randomized clinical trials has rendered the DAA-based regimens very attractive (Wyles et al., 2016; Flisiak et al., 2017). However, 'IFN-free'

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http://dx.doi.org/10.1016/j.ijid.2017.07.001

regimens still have high costs, therefore access to treatment with DAAs is limited by current reimbursement criteria in different countries (Craxì et al., 2016).

Only a few published studies on the efficacy and safety of DAAs in the real-world clinical setting are available, with particularly few related to HIV/HCV co-infected individuals (Milazzo et al., 2016; Bruno et al., 2017; Hawkins et al., 2016; Del Bello et al., 2016; Rockstroh et al., 2016; Younossi et al., 2016; Sogni et al., 2016). Therefore, the aim of this study was to assess the safety and effectiveness of DAA-based antiviral therapy in both HCV mono-infected and HIV/HCV co-infected patients in a clinical practice setting.

Materials and methods

All consecutive HCV-infected patients (≥18 years old), with or without HIV infection, who had received at least one dose of DAA-based anti-HCV therapy between February 2015 and September 2016 in the Clinic of Infectious Diseases of Bari, were included in this retrospective observational study.

Demographic, clinical (medical history, concomitant co-medications, failure with previous anti-HCV therapy, and adverse events), chemical, and virological data were collected for all subjects during the treatment period and after the end of treatment (EOT). Biochemical data collected included levels of serum creatinine, albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), haemoglobin, and the platelet count (PLT). Data regarding the history of HIV infection, CD4 cell count, and antiretroviral therapy (ART) were also retrieved for all HIV/HCV co-infected patients.

The primary end-point was the SVR12 rate (undetectability lasting for 12 consecutive weeks after the cessation of treatment) using an intention-to-treat (ITT) analysis; all patients who received at least one dose of anti-HCV medication were included in the analysis. The secondary end-point was the safety profile of DAAs during the treatment period.

DAA-based anti-HCV treatment

The following regimens were administered based on current guideline recommendations (EASL Recommendations on Treatment of Hepatitis C, 2016; Sogni et al., 2016): sofosbuvir (SOF; nucleoside NS5B polymerase inhibitor) + ribavirin (RBV) in genotypes 2 and 3; SOF and ledipasvir (LDV; NS5A inhibitor) ± RBV in genotypes 1 and 4; SOF and daclatasvir (DCV; NS5A inhibitor) ± RBV in genotypes 1, 2, and 3; SOF and simeprevir (SMV; NS3 protease inhibitor) ± RBV in genotypes 1 and 4; ombitasvir (OMB; NS5A inhibitor), paritaprevir/ritonavir (PTV/r; ritonavir-boosted protease inhibitor), and dasabuvir (DSV; non-nucleoside NS5B polymerase inhibitor) ± RBV in genotype 1; and OMB, PTV/r, and RBV in genotype 4.

RBV (weight-based RBV dose: <65 kg, 800 mg per day; ≥65 and <75 kg, 1000 mg per day; ≥75 kg, 1200 mg per day) was added according to the clinician's judgement and based on the international recommendations (EASL Recommendations on Treatment of Hepatitis C, 2016; European association for study of liver, 2015).

Assessment of liver fibrosis at baseline

Baseline liver fibrosis was assessed in all patients by means of surrogate biomarkers (fibrosis-4 score (FIB-4) and AST-to-PLT ratio index (APRI)) and by liver stiffness.

APRI was calculated according to the formula proposed by Wai (Wai et al., 2003) and FIB-4 was calculated using the Sterling formula (Sterling et al., 2006). An APRI score >1 and FIB-4 score ≥3.25 signifies advanced liver fibrosis or cirrhosis.

Liver stiffness was evaluated by certified operators (trained by the manufacturer) using transient elastography (FibroScan; EchoSens, Paris, France). Liver cirrhosis was defined as a liver stiffness ≥12.5 kPa (Castera et al., 2008), or in the presence of a clinical diagnosis.

HCV RNA measurement and HCV genotype assessment

Plasma HCV RNA levels were measured for all patients at baseline, at week 4, at EOT, and 3 and 6 months after EOT, using the Siemens Real Time PCR assay (Siemens Healthcare Diagnostics, Tarrytown, NY, USA), with a lower limit of detection of 15 IU/ml. HCV genotype and subtype were determined using the Siemens Versant HCV LiPA V2 assay (Siemens, Munich, Germany).

Definitions

Rapid virological response (RVR) was defined as an undetectable serum HCV RNA level at week 4 and SVR as an undetectable HCV RNA level at week 12 after EOT. Virological breakthrough was defined as an undetectable HCV RNA during treatment followed by a detectable HCV RNA, despite continued treatment. Relapse was defined as undetectable HCV RNA at EOT but detectable HCV RNA during follow-up.

Two consecutive HIV RNA measurements >200 copies/ml after virological suppression (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2017) signified virological failure to anti-HIV treatment. A virological blip was defined as an isolated detectable HIV RNA level after suppression, followed by a return to HIV RNA suppression.

Severe adverse events (SAEs)

Serious adverse events were classified according to a recent definition (Common Terminology Criteria for adverse events (CTCAE), 2017).

Ethics

This research did not require formal approval from the ethics committee according to Italian law, since it was performed as an observational retrospective study in the context of normal clinical routines. However, the study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. All patients provided informed consent for the use of their data for research purposes.

Statistical analysis

Descriptive statistics were calculated for demographic, clinical, and laboratory characteristics of cases. Mean and standard deviation (SD) values were recorded for normally distributed variables, and the median and interquartile range (IQR) were recorded for non-normally distributed variables. The number and percentage were recorded for categorical variables. Differences between groups were analysed using the Chi-square test, *t*-test, or Mann–Whitney test, as appropriate. Univariable and multivariable logistic regression models were applied to assess factors associated with a SVR and with the occurrence of SAEs. A p-value of <0.05 was considered to indicate significance.

Results

A total of 382 patients (320 HCV mono-infected and 62 HIV/HCV co-infected) were included in this study. The clinical

characteristics of these patients at baseline, whether HCV mono-infected or HCV/HIV co-infected, are summarized in Table 1.

All subjects were Caucasian. Compared with HCV mono-infected patients, HIV/HCV co-infected individuals were younger (median age 52.5 vs. 68 years, $p < 0.001$), mostly male (91.9% vs. 58.8%, $p < 0.001$), and more frequently infected with genotype 1a (51.6% vs. 6.3%, $p < 0.001$), genotype 3 (22.6% vs. 7.8%, $p < 0.001$), and genotype 4 (16.1% vs. 2.8%, $p < 0.001$). Failure to a previous anti-HCV treatment was reported in 208 patients (54.4%). Among the HCV treatment-experienced subjects, five had experienced failure with a previous IFN-free regimen. Interleukin 28 (IL-28) genotypes were available for 61 patients: 14 (22.9%) had a CC genotype, 29 (47.5%) had a CT genotype, and 18 (29.5%) had a TT genotype.

Cirrhosis was found in 256 (67%) patients (37 HIV/HCV co-infected). Most patients had compensated liver disease except two HCV mono-infected patients with Child–Pugh class C.

HIV/HCV co-infected subjects showed a higher Model for End-Stage Liver Disease (MELD) score and a lower PLT count at baseline compared with HCV mono-infected subjects. No differences in liver stiffness, APRI score, or FIB-4 score at baseline were observed between the two groups.

HCV mono-infected individuals were more likely to have two or more comorbidities than HIV/HCV co-infected patients before starting DAA treatment. Arterial hypertension (33%) and type 2 diabetes mellitus (16.8%) were the most common comorbidities.

HIV/HCV co-infected patients were more frequently treated with a DAA-based regimen without RBV compared to HCV mono-infected patients (66.2% vs. 46.7%, $p = 0.003$).

Safety profile of DAAs and factors associated with the occurrence of SAEs

Overall, DAA-based treatment was safe and well-tolerated in both HCV mono-infected and HIV/HCV co-infected patients. The safety profile is described in Table 2. The most common adverse events were rash (16.5%), fatigue (12%), and anaemia (11.5%). HIV/HCV co-infected patients were more likely to show jaundice and a PLT count $<70 \times 10^9$/l during treatment than HCV mono-infected patients. No

Table 1
Clinical characteristics at baseline of the 382 patients.[a]

	Total	HCV	HIV/HCV	*p*-Value
Number	*n* = 382	*n* = 320	*n* = 62	
Age, years	65 (53–73)	68 (58–75)	52.5 (51–55)	<0.001
Male, *n*	247 (64.6)	190 (59.3)	57 (91.9)	<0.001
BMI	25.9 (23.5–28.4)	26.1 (23.7–28.6)	25.6 (23–27.4)	0.02
HBsAg-positive	4 (1)	3 (0.9)	1 (1.6)	0.5
HCV genotypes				
1a	52 (13.6)	20 (6.3)	32 (51.6)	<0.001
1b	207 (54.2)	202 (63.1)	5 (8.1)	<0.001
2	65 (17)	64 (20)	1 (1.6)	<0.001
3a	39 (10.2)	25 (7.8)	14 (22.6)	<0.001
4	19 (5)	9 (2.8)	10 (16.1)	<0.001
HCV RNA, IU/ml	1 307 000 (390 400–3 080 000)	1 150 000 (377 050–3 043 769)	1 845 000 (680 925–3 879 500)	0.49
Treatment-experienced	208 (54.4)	171 (53.4)	37 (59.6)	0.22
Liver stiffness, kPa	13.6 (11.1–20.3)	13.5 (11.3–19)	13.9 (9.5–22.35)	0.98
FIB-4 score	3.36 (2.02–5.64)	3.43 (2.11–5.71)	2.77 (1.94–4.9)	0.1
APRI score	1.25 (0.68–2.28)	1.23 (0.68–2.15)	1.49 (0.77–2.78)	0.28
Cirrhosis, *n* (%)	256 (67)	219 (68.4)	37 (59.7)	0.18
Child–Pugh class				
A	244 (95.3)	209 (95.4)	35 (94.5)	0.18
B	10 (3.9)	8 (3.6)	2 (5.5)	0.74
C	2 (0.8)	2 (1)	0	0.53
MELD score	7 (7–8)	7 (7–8)	8 (7–9.7)	<0.001
Platelet count, $n \times 10^9$/l	141 (106–186.5)	143 (108–187)	137 (98.7–184.5)	0.33
Platelet count $<90 \times 10^9$/l	60 (15.7)	47 (14.7)	13 (21)	0.25
Albumin, g/dl	3.9 (3.7–4.2)	3.9 (3.7–4.2)	3.9 (3.7–4.2)	0.84
AST, IU/ml	66 (44.5–96.5)	66 (44–94)	65.5 (48.7–101.5)	0.91
ALT, IU/ml	77 (51–130)	74 (50–125)	93.5 (57–141.5)	0.04
≥2 comorbidities	99 (25.9)	91 (28.4)	8 (12.9)	0.01
Type of HCV therapy				
SOF + RBV	75 (19.6)	63 (19.7)	12 (19.4)	0.95
SOF + SMV ± RBV	57 (14.9)	40 (12.5)	17 (27.4)	0.002
SOF + LDV ± RBV	64 (16.8)	42 (13.1)	12 (19.4)	0.19
SOF + DCV ± RBV	37 (9.7)	31 (9.7)	6 (9.6)	0.81
OMB + PTV/r + DAS ± RBV	141 (36.9)	129 (40.3)	12 (19.4)	0.001
OMB + PTV/r + RBV	8 (2.1)	5 (1.6)	3 (4.8)	0.1
Duration of HCV therapy				
12 weeks	254 (66.5)	216 (67.5)	38 (61.3)	0.34
16 weeks	15 (3.9)	15 (4.7)	0	0.08
24 weeks	108 (28.3)	85 (26.6)	23 (37.1)	0.09
Other	5 (1.3)	4 (1.3)	1 (1.6)	0.81
Addition of RBV	241 (63)	212 (66.2)	29 (46.7)	0.003
Patients on ART			60 (96.8)	
CD4 nadir, cells/mm^3			124.5 (68.25–223.25)	
Change of ART			23 (37.1)	
Undetectable HIV RNA			61 (98.4)	
CD4 count, cells/mm^3			611 (414–843.5)	

ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; DAS, dasabuvir; DCV, daclatasvir; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LDV, ledipasvir; MELD, Model for End-Stage Liver Disease; OMB, ombitasvir; PTV/r, paritaprevir/ritonavir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

[a] Results are presented as frequencies (%) for qualitative values and median (interquartile range) for quantitative values.

Table 2
Safety of treatment with DAAs.

	Total, $n=382$	HCV, $n=320$		HIV/HCV, $n=62$		p-Value
		RBV	No RBV	RBV	No RBV	
Number according to RBV use		212	108	29	33	
Most common adverse events						
Headache	29 (7.6)	16 (7.5)	7 (6.4)	2 (6.9)	4 (12.1)	0.75
Insomnia	12 (3.1)	8 (3.7)	2 (1.8)	1 (3.4)	1 (3)	0.83
Fatigue	46 (12)	30 (14.1)	5 (4.6)	8 (27.5)	3 (9)	0.003
Dizziness	14 (2.7)	8 (3.7)	5 (4.6)	0	1 (3)	0.69
Mood disorders	27 (7.1)	18 (8.5)	3 (2.7)	3 (10.3)	3 (9)	0.22
Gastrointestinal disorders	41 (10.7)	31 (14.6)	6 (5.5)	2 (6.9)	2 (6)	0.05
Rash, pruritus, or photosensitivity reaction	63 (16.5)	38 (17.9)	16 (14.1)	3 (10.3)	6 (18.1)	0.7
Jaundice	10 (2.6)	4 (1.8)	0	6 (20.6)	0	<0.0001
Other	62 (16.2)	32 (15.1)	25 (23.1)	1 (3.4)	4 (12.1)	0.05
Haematological abnormalities						
Any grade of anaemia	44 (11.5)	36 (16.9)	2 (1.8)	6 (20.6)	0	<0.0001
Anaemia <10 g/dl	30 (7.9)	22 (10.3)	2 (1.8)	6 (20.6)	0	<0.0001
Anaemia <8 g/dl	6 (1.6)	5 (2.3)	1 (0.9)	0	0	0.54
Use of erythropoietin	16 (4.2)	12 (5.6)	1 (0.9)	3 (10.3)	0	0.04
RBV dose reduction	26 (6.8)	25 (11.7)	0	1 (3.4)	0	<0.0001
Blood transfusions	5 (1.3)	4 (1.8)	1 (0.9)	0	0	0.02
Platelet count $<70\times10^9$/l	31 (8.1)	14 (6.6)	7 (6.4)	2 (6.8)	8 (24.2)	0.005
Platelet count $<50\times10^9$/l	9 (2.4)	3 (1.4)	3 (2.7)	0	3 (9)	0.04
Biochemical abnormalities						
Elevated total bilirubin (4–5 vv)	20 (5.2)	9 (4.2)	7 (6.4)	6 (20.6)	1 (3)	0.005
Discontinuation of therapy	10 (2.6)	5 (2.3)	4 (3.7)	0	1 (3)	0.71
At least 1 adverse event	220 (57.6)	133 (62.7)	50 (46.2)	19 (65.5)	18 (54.5)	0.03
≥2 adverse events	87 (22.8)	56 (26.4)	17 (15.7)	10 (34.4)	4 (12.1)	0.02
Severe adverse events	17 (4.5)	10 (4.7)	5 (4.6)	1 (3.4)	1 (3)	0.96
Gastrointestinal haemorrhage	4 (1)	3 (1.4)	0	1 (3.4)	0	0.33
Severe anaemia	5 (1.3)	4 (1.8)	1 (0.9)	0	0	0.32
Hepatic encephalopathy	2 (0.5)	1 (0.5)	1 (0.9)	0	0	0.87
Other	6 (1.6)	2 (1)	3 (2.7)	0	1 (3)	0.47
Deaths	2 (0.5)	1 (0.5)	1 (0.9)	0	0	0.87

DAA, directly acting antiviral; HCV, hepatitis C virus; RBV, ribavirin; ULN, upper limit normal.

other significant differences in terms of the occurrence of adverse events were observed between the two groups. In addition, patients receiving RBV more frequently showed adverse events in the course of treatment in comparison with subjects treated with RBV-sparing regimens. Erythropoietin use and a RBV dose reduction were reported in 16 (4.2%) and 26 (6.8%) patients, respectively. Five patients (1.3%) needed blood transfusions.

SAEs occurred in 17 patients (4.5%) and a discontinuation of anti-HCV treatment was observed in 10 (2.6%) individuals overall. One HCV mono-infected patient, who achieved a SVR, stopped therapy because of liver transplantation. One HIV/HCV co-infected patient with HCV genotype 4 who was treated with SOF + LDV experienced a virological breakthrough at week 8 and discontinued anti-HCV therapy. Of the 17 patients with SAEs, 14 required hospitalization. The most common SAEs were severe anaemia in five patients (1.3%) and gastrointestinal bleeding in four (1%). Two patients developed newly diagnosed atrial fibrillation.

A baseline PLT count $<90\times10^9$/l (odds ratio (OR) 5.34, 95% confidence interval (CI) 1.97–14.49, $p=0.001$), a baseline albumin <3.5 g/dl (OR 4.3, 95% CI 1.5–12.27, $p=0.006$), and a MELD score >10 (OR 7.4, 95% 1.82–30.3, $p=0.005$) were associated with the occurrence of SAEs on univariate analysis. However, on multivariable analysis adjusting for a MELD score >10 and PLT count $<90\times10^9$/l, a baseline MELD score >10 was the only factor significantly associated with SAEs (OR 4.78, 95% CI 1.02–22.53, $p=0.04$).

Two deaths (0.5%) were reported during anti-HCV therapy (due to bleeding oesophageal varices and non-Hodgkin lymphoma).

Effectiveness of DAAs and factors associated with SVR12

Overall, SVR12 was achieved in 365/382 (95.5%) patients in the ITT analysis. SVR rates according to the use of RBV, diagnosis of cirrhosis, failure on a prior HCV treatment, concomitant HIV infection, and HCV genotype 3 infection are shown in Figure 1.

Factors associated with SVR are described in Table 3. Patients with a baseline PLT count $<90\times10^9$/l (OR 4.12, 95% CI 1.5–11.3, $p=0.006$), a liver stiffness >20 kPa (OR 3.05, 95% CI 1.03–8.96, $p=0.04$), a MELD score >10 (OR 5.26, 95% CI 1.16–23.89, $p=0.03$), and a genotype 3 infection (OR 5.48, 95% CI 1.9–15.7, $p=0.002$) were less likely to achieve SVR. Female sex (OR 0.1, 95% CI 0.01–0.82, $p=0.03$) was associated with higher rates of SVR. On multivariable analysis, adjusting for sex, liver stiffness >20 kPa, PLT count $<90\times10^9$/l, MELD score >10, and genotype 3 infection, only genotype 3 infection remained independently associated with a lower rate of SVR (OR 21.64, 95% CI 3.81–123, $p=0.001$).

SVR12 rates according to the DAA regimen were as follows: 89.3% (67/75) for SOF + RBV, 94.7% (54/57) for SOF + SMV ± RBV, 93.7% (60/64) for SOF + LDV ± RBV, 97.3% (36/37) for SOF + DCV ± RBV, 99.3% (140/141) for OMB + PTV/r + DAS ± RBV, and 100% (8/8) for OMB + PTV/r + RBV.

SVR12 rates according to the HCV genotype were as follows: 98% (51/52) for genotype 1a, 98% (203/207) for genotype 1b, 93.8% (61/65) for genotype 2, 84.6% (33/39) for genotype 3, and 89.4% (17/19) for genotype 4.

SVR12 rates according to the DAA regimen for the 39 patients infected with genotype 3 were as follows: 78.9% (15/19) for a 24-week course of SOF + RBV, 75% (3/4) for a 24-week course of SOF + DCV, 100% (4/4) for a 12-week course of SOF + DCV + RBV, and 100% (8/8) for a 24-week course of SOF + DCV + RBV.

An additional patient, wrongly classified as infected with genotype 1b, received a 12-week course of SOF + SMV + RBV and relapsed, because after repeat HCV genotyping the patient was actually found to have a genotype 3 infection.

All patients who had experienced previous failure with an IFN-sparing regimen achieved SVR12.

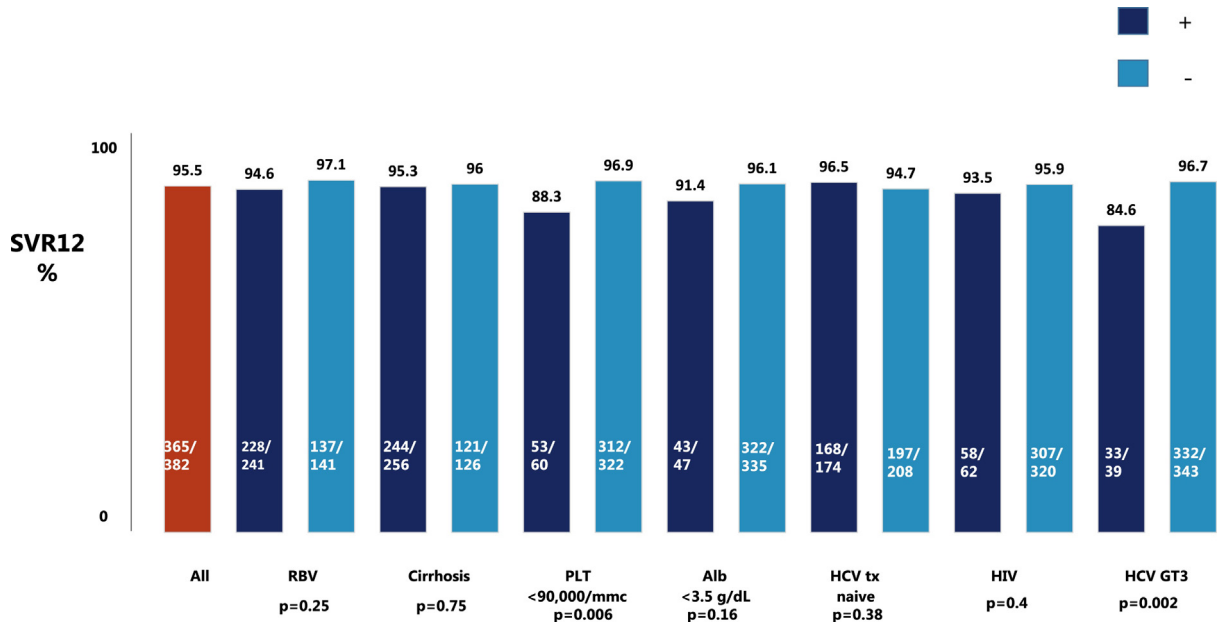

Figure 1. SVR12 rates according to the use of RBV, diagnosis of cirrhosis, platelet count, albumin level, previous anti-HCV therapy, HIV infection, and HCV genotype 3 vs. other genotypes. Abbreviations: SVR12, sustained virological response (undetectability lasting for 12 consecutive weeks after the cessation of treatment); RBV, ribavirin; GT, genotype.

Among the 17 patients who did not achieve SVR12, two HCV mono-infected patients were lost to follow-up, five discontinued therapy (four for SAEs, including two deaths, and one genotype 4 HIV/HCV co-infected patient treated with SOF + LDV who had virological breakthrough), and 10 had a relapse: two genotype 2 and four genotype 3 treated with SOF and RBV; one genotype 1b treated with OMB + PTV/r + DAS; one genotype 1b and one genotype 4 both treated with SOF + SMV; and one HCV genotype 3 patient wrongly treated with SOF + SMV + RBV for 12 weeks.

Patients who did not achieve SVR, including those with virological relapse and breakthrough, underwent resistance analysis. Resistance-associated variants (RAVs) are shown in Table 4.

Change of ART

Among the 62 HIV/HCV co-infected individuals, 60 (96.7%) were on ART at the initiation of DAA treatment and 23/60 (37%) required a change of ART because of drug–drug interactions. Patients treated with SOF + SMV (12/23, 52.1%) and OMB + PTV/r + DAS + RBV (9/23, 39.1%) were more likely to change ART before starting DAA treatment. Tenofovir/emtricitabine, raltegravir, rilpivirine, and unboosted atazanavir (for patients treated with OMB + PTV/r + DAS + RBV) were the antiretrovirals most used in patients modifying ART. Of the 23 patients who changed ART, nine returned to their previous ART regimen after the end of DAA treatment. At the end of anti-HCV therapy, only one subject, who did not change ART, had a detectable HIV RNA (46 copies/ml). Six patients showed a detectable HIV RNA (two with >200 copies/ml) at 3 months after EOT, but all had achieved viral suppression at the next visit. No virological failure was observed.

Occurrence of HCC after EOT

Hepatocellular carcinoma (HCC) occurred in six HCV mono-infected patients with compensated cirrhosis (1.5%) after EOT. Abdominal ultrasonography performed within 6 months before the initiation of DAA showed no evidence of HCC in any of the patients. Five of six HCC patients achieved SVR12 (four with genotype 1b and one with genotype 1a) and developed HCC within 12 months after EOT. One of these patients died from HCC progression at 15 months after EOT. One HCV genotype 2-infected

Table 3
Factors associated with lower rates of sustained virological response (SVR).

Baseline variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Sex, female vs. male	0.10	0.014–0.822	0.03	0.16	0.02–1.25	0.08
HIV infection, yes vs. no	1.63	0.513–5.171	0.40			
Age >65 years, yes vs. no	0.52	0.19–1.449	0.21			
Use of RBV, yes vs. no	1.95	0.624–6.109	0.25			
Cirrhosis, yes vs. no	1.19	0.41–3.455	0.75			
Liver stiffness >20 kPa, yes vs. no	3.05	1.038–8.966	0.04	1.61	0.42–6.22	0.48
Platelet count $<90 \times 10^9$/l, yes vs. no	4.12	1.503–11.301	0.006	3.63	0.91–14.46	0.06
Albumin, <3.5 vs. >3.5 g/dl	2.30	0.719–7.387	0.16			
MELD >10 vs. <10, yes vs. no	5.27	1.161–23.892	0.03	4.20	0.70–25.43	0.11
RVR, yes vs. no	0.94	0.201–4.391	0.93			
HCV treatment-experienced, yes vs. no	1.56	0.566–4.318	0.38			
Genotype 3 vs. others genotypes, yes vs. no	5.49	1.907–15.794	0.002	21.64	3.81–123	0.001

CI, confidence interval; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; OR, odds ratio; RBV, ribavirin; RVR, rapid virological response.

Table 4
Clinical characteristics of the 17 patients who did not achieve a sustained virological response (SVR).

No.	HIV-pos	Age (years)	Sex	BL HCV RNA IU/ml	GT	Cirrhosis	CP	Previous therapy	Therapy	Treatment duration (weeks)	Cause for TD	Outcome	RAV NS3 At TF	RAV NS5A At TF	RAV NS5B At TF
1	No	83	M	3 916 000	1b	Yes	B	PR	SOF + LDV + RBV	8	Bleeding oesophageal varices	Death	NA	NA	NA
2	No	55	M	49 380	3a	Yes	B	Naive	SOF + DCV	2	Non-Hodgkin lymphoma	Death	NA	NA	NA
3	No	73	M	537 400	2	Yes	A	PR	SOF + RBV	4	Diffuse rash	TD	NA	NA	NA
4	No	41	M	10 200 000	1a	Yes	A	Naive	SOF + LDV + RBV	12		L-FU	NA	NA	NA
5	No	83	M	290 200	2	No		Naive	SOF + RBV	4	Severe anaemia	TD	NA	NA	NA
6	No	60	M	1 950 000	1b	Yes	A	TVR/PR	SOF + LDV + RBV	24		L-FU	NA	NA	NA
7	Yes	52	M	359 700	4	No		PR	SOF + LDV	8	Virological breakthrough	TD	NA	None	None
8	Yes	52	M	2 552 000	3a	Yes	A	PR	SOF + RBV	24		Relapse	NA	None	None
9	No	55	M	2 173 000	1b	Yes	B	PR	SOF + SMV	12		Relapse	L36 V, D168 V, I170V	None	C451Y, S556G
10	No	57	M	1 592 000	3a	Yes	A	PR	SOF + RBV	24		Relapse	NA	NA	None
11	No	69	M	3 200 000	2	Yes	A	Naive	SOF + RBV	16		Relapse	NA	NA	NA
12	No	50	M	771 200	3a	No		PR	SOF + SMV + RBV	12		Relapse	NA	NA	None
13	No	77	M	4 697 000	1b	No		Naive	OMB + PTV/r + DAS	12		Relapse	Q80L, D168V	Y93YH	C316N, C451N, S556G, L159F
14	No	47	M	107 200	3a	Yes	A	PR	SOF + RBV	24		Relapse	NA	None	None
15	Yes	53	M	568400	4	Yes	A	PR	SOF + SMV	12		Relapse	None	None	None
16	No	67	F	211800	2	No		Naive	SOF + RBV	12		Relapse	NA	NA	NA
17	Yes	51	M	2650000	3a	Yes	A	PR	SOF + RBV	24		Relapse	NA	NA	None

BL, baseline; CP, Child–Pugh class; DAS, dasabuvir; DCV, daclatasvir; F, female; GT, genotype; HCV, hepatitis C virus; LDV, ledipasvir; L-FU, lost to follow-up; M, male; NA, not available; OMB, ombitasvir; PR, pegylated interferon and ribavirin; PTV/r, paritaprevir/ritonavir; RAVs, resistance-associated variant; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TD, treatment discontinuation; TF, treatment failure; TVR, telaprevir.

patient, who did not attain a SVR, had a negative abdominal computed tomography performed before anti-HCV therapy (SOF + RBV for 16 weeks) because of a high level of alpha-fetoprotein at baseline (47.6 ng/ml). Three months after the EOT, the patient developed HCC.

Discussion

Recent real-world studies have reported high safety and efficacy rates for DAAs, confirming the results already observed in randomized clinical trials (Wyles et al., 2016; Flisiak et al., 2017). However, real-world data for HIV/HCV co-infected patients appear to be limited (Milazzo et al., 2016; Bruno et al., 2017; Hawkins et al., 2016; Del Bello et al., 2016; Rockstroh et al., 2016; Younossi et al., 2016; Sogni et al., 2016), and only two studies have included both HIV/HCV co-infected patients and HCV mono-infected individuals (Milazzo et al., 2016; Bruno et al., 2017). Despite the retrospective nature of this study, which represents its main limitation, these data from a large single-centre cohort including patients with HIV/HCV co-infection confirm that different DAA-based regimens are extremely effective and safe. Moreover, factors associated with the achievement of SVR were evaluated.

In agreement with others studies (Milazzo et al., 2016; Bruno et al., 2017; Hawkins et al., 2016; Del Bello et al., 2016; Rockstroh et al., 2016; Younossi et al., 2016; Sogni et al., 2016), no differences were observed in terms of SVR between patients with and without cirrhosis. However, patients with a baseline PLT count $<90 \times 10^9$/l were less likely to achieve HCV eradication compared to those with a PLT count $\geq 90 \times 10^9$/l. The PLT count is considered an indirect marker of portal hypertension, and a low PLT count has been associated with advanced liver fibrosis and cirrhosis in real-life cohorts (Marot et al., 2016); in particular, a cut-off PLT count of $<90 \times 10^9$/l has been demonstrated to be a strong predictor of SVR (Lawitz et al., 2016). Conversely, a baseline albumin level <3.5 g/dl, a marker of liver synthesis, was not associated with lower rates of SVR in the present patient cohort. This is in contrast with other studies, in which a baseline albumin <3.5 g/dl was associated with failure of anti-HCV treatment (Maan et al., 2016). This could probably be explained by the limited number of patients with advanced liver cirrhosis in the present study group (Child–Pugh class B and C).

Moreover, the use of RBV did not seem to have an impact on the achievement of SVR. This is not surprising in clinical practice, as RBV was added to IFN-free regimens only in 'difficult to treat' patients, including those with decompensated liver disease, those failing a prior treatment with DAAs, and genotype 1a-infected individuals receiving certain combinations, according to international guidelines and clinical judgement (EASL Recommendations on Treatment of Hepatitis C, 2016; Feld et al., 2017).

Although a high overall SVR rate was observed (95.5%), genotype 3-infected patients were more likely to fail DAA treatment in comparison to those infected with other genotypes. In fact, genotype 3 infection was the only significant factor associated with a lower rate of SVR in both the univariate and multivariate analysis. However, in this cohort, genotype 3-infected patients with cirrhosis for whom anti-HCV treatment could not be further delayed, were treated with the combination of SOF + RBV for 24 weeks, which is currently considered suboptimal, because of the non-availability of daclatasvir until September 2015. This could possibly explain the lower rate of SVR in this group. In agreement with the study data, lower rates of SVR in genotype 3-infected patients have been described previously (Werner et al., 2016), and recent data suggest that genotype 3-infected patients with cirrhosis are at higher risk of hepatic decompensation during DAA-based treatment in comparison to those infected with other genotypes (Maan et al., 2016). Furthermore, the present study cohort included only a small number of genotype 3-infected patients; therefore, larger studies should be performed to confirm

these observations. A recent real-world study reported the high efficacy of the combination of SOF with an NS5A inhibitor (DCV or LDV) in genotype 3-infected patients with compensated or decompensated cirrhosis (Alonso et al., 2016). However, in the near future, further combinations will be available for the treatment of genotype 3 infections (Foster et al., 2015; Gane et al., 2016).

In the present study cohort, male sex was associated with lower SVR rates than female sex in the univariate analysis, but this difference was not confirmed on multivariate analysis. However, only 17 patients did not achieve SVR, thus definitive conclusions cannot be drawn.

Furthermore, differences in the genotype distribution were observed between HCV mono-infected and HIV/HCV co-infected individuals. In fact, as expected, genotype 1a and genotype 3 were found widely in HIV/HCV co-infected patients, in whom HCV transmission was mainly due to intravenous drug use, whereas HCV mono-infected subjects were mostly infected with genotype 1b and genotype 2, which are largely distributed in Europe (Hajarizadeh et al., 2013; EASL Recommendations on Treatment of Hepatitis C, 2016).

Of note, no significant difference in effectiveness was observed between HCV mono-infected and HIV/HCV co-infected individuals (95.9% vs. 93.5%; $p = 0.4$), thus confirming the excellent efficacy of DAAs. HIV/HCV co-infected patients showed a higher baseline MELD score compared to HCV mono-infected patients. A possible explanation could be the impact of certain antiretroviral drugs (13 patients were on atazanavir-based ART), which, by increasing indirect bilirubin, modified the baseline MELD score without clinical significance. RBV was frequently not included in HIV/HCV co-infected individuals for various reasons. Firstly, the addition of RBV was based on the clinician's judgement and the clinical history of each patient. Secondly, 10 patients (16%) had a previous history of RBV intolerance or a contraindication to its use. Thirdly, due to the reduced adherence to a treatment including a large number of pills, RBV-sparing regimens were possibly preferred in HIV/HCV co-infected individuals. In addition, HIV/HCV co-infected patients in the study cohort did not have more advanced liver disease compared to HCV mono-infected patients. Although this may not represent the only reason for preferring an RBV-free combination, some regimens have been demonstrated to be extremely effective regardless of the use of RBV, particularly in patients without advanced cirrhosis. Nevertheless, the reduced use of RBV in the HIV/HCV co-infected group did not have an impact on the achievement of SVR.

This study provides further information regarding changes in ART and their impact on immunological and virological parameters in HIV/HCV co-infected patients. Despite 23 patients (37%) needing a modification of their ART due to drug–drug interactions, no virological failure was observed for the HIV infection. These data are similar to those described in a recent study in which changes of ART did not have a negative impact on HIV RNA suppression (Andreoni et al., 2016).

Currently, HIV/HCV co-infected individuals are no longer considered a 'special population', even though there remain certain barriers to the treatment of these patients. In fact, social and behavioural issues, drug–drug interactions between DAAs and ART, and high rates of HCV re-infection require a dedicated medical team with expertise in the management of HIV/HCV co-infected patients (Sulkowsky, 2016).

Overall, DAA-based treatment was safe. RBV use was associated with more adverse events in the course of treatment in comparison to those treated with RBV-sparing regimens. SAEs occurred in only 17 patients (4.5%), and treatment discontinuation was reported in 10 individuals (2.6%). These data are similar to those described in other studies (Werner et al., 2016; Alonso et al., 2016). Patients with a PLT count $<90 \times 10^9$/l, albumin level <3.5 g/dl, and MELD score >10 were found to be more likely to have SAEs on univariate analysis. On multivariate analysis, a MELD score >10 was the only factor associated with the occurrence of SAEs, suggesting that patients with advanced liver cirrhosis could be at higher risk of SAEs. However, the baseline MELD score was available for only 184 subjects and this could represent a limitation in the analysis.

In this cohort, 192 individuals (50.2%) were >65 years of age and had a high burden of comorbidities and co-medications. Despite these issues, overall DAA-based treatment was well-tolerated and high rates of SVR were reported even in this population, in agreement with recent studies evaluating the impact of DAAs in elderly populations (Vermehren et al., 2016; Conti et al., 2016a; Fabrizio et al., 2017).

Six cases of HCC were reported within 1 year after the end of treatment and five occurred despite the achievement of SVR. Currently, the onset of HCC following DAA-based treatment represents a debated and controversial topic (Cammà et al., 2016). Although some studies have revealed an increased risk of HCC developing after DAA-based treatment (Reig et al., 2016; Conti et al., 2016b), others have not confirmed this trend (Nault and Colombo, 2016; ANRS Collaborative Study Group on Hepatocellular Carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts), 2016). A possible explanation for the higher evidence of HCC after DAA-based treatment might be the fact that, thanks to the availability of DAAs, the possibilities for treating subjects with advanced or decompensated cirrhosis have been considerably extended. In these patients with advanced liver disease, the carcinogenesis process might already have started, even if it was not evidenced with routine imaging methods before the beginning of anti-HCV therapy.

This study has some limitations, including its observational nature and the limited follow-up period after treatment. Moreover, a large study reported lower rates of SVR12 than observed in clinical trials in patients with compensated or decompensated cirrhosis (Maan et al., 2016). In the present study cohort, however, only two patients had decompensated cirrhosis and the impact of DAAs in this group could not be fully assessed.

In conclusion, these data confirm the high efficacy and safety of DAA-based treatment in both HCV mono-infected and HIV/HCV co-infected patients from a large real-world setting. The beneficial effects of DAA-induced HCV eradication should be evaluated over longer follow-up, in terms of the reduction of liver- and non-liver-related morbidity and mortality and assessing the improvement in quality of life in patients achieving SVR.

Conflict of interest

None declared.

Acknowledgements

The results of this study were presented in part as a poster (P287) at the HIV Drug Therapy Congress, Glasgow, UK, October 23–26, 2016.

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