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Safety and effectiveness of a 12-week course of sofosbuvir and simeprevir ± ribavirin in HCV-infected patients with or without HIV infection: a multicentre observational study ☆

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ABSTRACT

The combination of sofosbuvir and simeprevir ± ribavirin (SOF + SMV ± RBV) for hepatitis C virus (HCV) treatment has been associated with high rates of sustained virological response (SVR). Few data are available regarding this regimen in HIV/HCV co-infected patients. This study evaluated the effectiveness and safety of a 12-week course of SOF + SMV ± RBV in a cohort of HCV monoinfected and HIV/HCV co-infected individuals. HCV-infected patients, with or without HIV infection, receiving a 12-week course of SOF + SMV ± RBV in four Italian centres from February to October 2015, were included in this retrospective observational study. Clinical and biochemical data were retrieved for all patients. A total of 88 individuals were evaluated: 29 (33.0%) HIV/HCV co-infected and 59 (67.0%) monoinfected. Most patients were males with HCV genotype 1b (62.5%) and 1a (25%) infection. RBV was used in 41 HCV monoinfected and 6 HIV/HCV co-infected patients. Cirrhosis was found in 67 patients (76.1%). The most common adverse events (AEs) were rash and/or pruritus (23.9%), fatigue (13.6%) and anaemia (9.1%). Serious AEs occurred in three patients (3.4%). No treatment discontinuations were observed. RBV use was associated with multiple AEs ($P = 0.02$). An overall SVR12 of 93.2% was achieved; 96.6% in HCV monoinfected and 86.2% in HIV/HCV co-infected individuals, without significance both in univariate ($P = 0.09$) and multivariate analyses ($P = 0.12$). A baseline platelet count ≥90 000/mm^3 was associated with higher rates of SVR ($P = 0.005$). A 12-week course of SOF + SMV ± RBV was associated with good safety and high SVR12 rate both in HCV monoinfected and HIV-HCV co-infected individuals.

1. Introduction

Worldwide, chronic hepatitis C virus (HCV) infection is one of the most relevant causes of liver-related morbidity and mortality [1]. The introduction of direct-acting antivirals (DAAs) has revolutionised HCV treatment, leading to higher rates of sustained virological response (SVR) (>90% in the majority of patients) compared with pegylated interferon (peg-IFN)-based therapy in HCV-infected patients with or without human immunodeficiency virus (HIV) infection [2,3]. In addition, 'IFN-free' regimens have been demonstrated to be extremely safe and well tolerated, but they still have high costs and access is limited according to the current reimbursement criteria in different countries.

The combination of sofosbuvir (SOF) and simeprevir (SMV) with or without ribavirin (RBV) for 12 weeks was one of the first 'IFN-free' regimens available for treating patients infected with HCV genotypes 1 (HCV-1) and 4 (HCV-4) [4,5].

Although several studies have reported high rates of SVR with SOF + SMV ± RBV in HCV monoinfected patients [6–10], to our knowledge no phase 3 randomised trials have been performed in HIV/HCV co-infected patients, and only few 'real-life' data are available regarding the impact of the SOF + SMV ± RBV regimen in this population [11,12].

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Hence, the aim of this study was to evaluate the effectiveness and safety of a 12-week course of SOF + SMV ± RBV in HCV monoinfected and HIV/HCV co-infected individuals from a multicentre cohort.

2. Materials and methods

HCV-infected patients (age >18 years), with or without HIV infection, receiving 12 weeks of treatment with SOF + SMV ± RBV in four Apulian centres (Italy) from February to October 2015 were included in this retrospective observational study.

Demographic, clinical (medical history, failure of previous anti-HCV therapy and adverse events) and biochemical data were retrieved for all subjects throughout the treatment period and at 3 months and 6 months after the end of treatment (EOT). Laboratory data included levels of serum creatinine, albumin, total bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), haemoglobin and platelets. Data regarding history of HIV infection, CD4 cell count and antiretroviral therapy (ART) were recorded for all HIV/HCV co-infected patients.

All patients received a 12-week course of SOF (400 mg orally once daily) and SMV (150 mg orally once daily) with or without RBV for 12 weeks according to the clinician's judgement (RBV dose based upon body weight: < 65 kg, 800 mg/day; ≥65 and <80 kg, 1000 mg/day; and ≥80 kg, 1200 mg/day, split in two doses daily).

Rapid virological response (RVR) and SVR were defined as undetectable HCV-RNA at Week 4 and after 12 weeks from the EOT. A virological relapse was defined when HCV-RNA was undetectable at the EOT but detectable after EOT.

The presence of two consecutive HIV-RNA levels of >200 copies/mL after virological suppression was considered a virological failure in HIV treatment. A virological blip was considered an isolated detectable HIV-RNA level after virological suppression that was followed by a return to virological suppression [13].

2.1. Liver fibrosis assessment at baseline

Liver fibrosis at baseline was determined by means of surrogate biomarkers [fibrosis index based on four factors (FIB-4) and AST-to-platelet ratio index (APRI) scores] and by liver stiffness using transient elastography (FibroScan; EchoSens, Paris, France).

The APRI score was calculated using Wai's formula [14]: (AST/upper limit of normal considered as 40 IU/L)/platelet count (expressed as platelets × 10^9/L) × 100. The FIB-4 score was calculated using Sterling's formula [15] as follows: age [years] × AST [IU/L]/platelet count [expressed as platelets × 10^9/L] × (ALT1/2[IU/L]). An APRI score >1 and FIB-4 ≥ 3.25 were associated with advanced liver fibrosis or cirrhosis.

Liver stiffness was evaluated by certified operators (trained by the manufacturer) using transient elastography. Liver cirrhosis was defined as FibroScan ≥ 12.5 kPa [16] or in the presence of a clinical diagnosis.

2.2. HCV-RNA measurement

Quantitative HCV-RNA was measured for all patients at baseline, at Week 4, at EOT, and 3 months and 6 months after EOT. HCV-RNA was measured using a Siemens real-time PCR assay (Siemens Healthcare Diagnostics, Tarrytown, NY) with a lower limit of detection of 15 IU/mL, or an Abbott RealTime HCV Assay (Abbott Molecular Inc., De Plaines, IL, USA) with a lower limit of detection of 12 IU/mL.

2.3. Statistics

Descriptive statistics were calculated for demographic, clinical and laboratory characteristics. The mean ± standard deviation is presented for normally distributed variables, the median and interquartile range for non-normally distributed variables, and the number and percentage for categorical variables. Groups were compared by parametric or non-parametric tests according to data distribution for continuous variables, and by Pearson's χ^2 test (Fisher's exact test where appropriate) for categorical variables. Univariable and multivariable logistic regression models were applied to assess factors associated with SVR. A *P*-value of <0.05 was considered statistically significant.

2.4. Ethics

The 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.

3. Results

3.1. Baseline characteristics of enrolled patients

A total of 88 patients were included in the study, comprising 29 (33.0%) HIV/HCV co-infected patients and 59 (67.0%) HCV monoinfected patients. All subjects were Caucasian. Clinical characteristics at baseline for the two groups are described in Table 1. Most patients were male (64/88; 72.7%) with HCV-1b (55/88; 62.5%) and HCV-1a (22/88; 25.0%); 10 were infected with HCV-4 and 1 with HCV-5. Q80K polymorphism was tested in only 14 HCV-1a-infected subjects, but no patient harboured it. Interleukin-28 (IL-28) genotypes were available for 33 patients: 8 CC (24.2%), 16 CT (48.5%) and 9 TT (27.3%). A failure of previous anti-HCV treatment was reported in 49 patients (55.7%).

RBV was added to the regimen in 47 patients (47/88; 53.4%), mostly in HCV monoinfected (41/59; 69.5%) compared with HIV/HCV co-infected (6/29; 20.6%) patients.

HIV/HCV co-infected subjects were younger ($P = 0.001$) and were more frequently infected with HCV-1a compared with HCV monoinfected subjects (58.6% vs. 8.5%; $P < 0.001$).

Cirrhosis was found in 67 patients (76.1%), including 43 (72.9%) HCV monoinfected and 24 (82.8%) HIV/HCV co-infected patients. All cirrhotic patients had compensated liver disease. Only two patients had Child–Pugh score B.

No differences in terms of AST and ALT levels, albumin, HCV-RNA quantitative, diagnosis of cirrhosis, liver stiffness and FIB-4 score were observed between the two groups at baseline. However, HIV/HCV co-infected patients showed a lower platelet count ($P = 0.01$) and a higher APRI score ($P = 0.04$) before starting therapy.

Diabetes mellitus type 2 and arterial hypertension were the most common baseline co-morbidities and were observed in 12 (13.6%) and 17 (19.3%) individuals, respectively.

3.2. Safety of the combination of sofosbuvir and simeprevir ± ribavirin (SOF + SMV ± RBV)

The combination of SOF + SMV ± RBV was overall safe and well tolerated. The safety profile of SOF + SMV ± RBV in HCV patients with or without HIV infection is described in Table 2. Most common adverse events (AEs) were pruritus (14.7%), fatigue (13.6%), rash (9%, grades 1–2 only) and anaemia (9.1%). However, only three patients showed