

# Sofosbuvir-based therapies in genotype 2 hepatitis C virus cirrhosis: A real-life experience with focus on ribavirin dose

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## Abstract

This study aimed to investigate the efficacy and safety of sofosbuvir-based therapies for the treatment of cirrhosis from hepatitis C virus (HCV) genotype 2 infection. Data of all consecutive HCV genotype 2 cirrhotic patients who started sofosbuvir-based treatments between January 2015 and March 2017 in eight Italian tertiary hospitals were collected retrospectively. Overall, 273 patients (Child A: 94.5%) were enrolled. In the 194 subjects treated with sofosbuvir/ribavirin, median initial ribavirin dosage was 13.9 mg/kg/day, and therapy duration was 16 weeks. Sustained virological response (SVR) rates were 93.8% in intention-to-treat (ITT) and 95.3% in per-protocol (PP) analyses for the 129 treatment-naïve patients, and 96.9% (ITT) and 98.4% (PP) for the 65 treatment-experienced subjects. Adverse events were reported in 142 patients (73.2%), but only 1.5% discontinued treatment. Eighty-eight subjects with treatment-induced anemia (mild: 34.5%, moderate: 7.7%, severe: 3.1%) had to reduce ribavirin dosage, but SVR rates were comparable to the weight-based dose group, both in ITT (95.4% and 94.3%) and PP (97.7% and 95.2%) analyses, respectively. Moreover, ITT and PP SVR rates were similar between shorter (<20 weeks) (94.1% and 96.0%, respectively) and prolonged (≥20 weeks) regimens (95.7% and 96.7%, respectively). SVR rates in the 79 subjects treated with sofosbuvir/daclatasvir (without ribavirin) were similar (ITT: 96.2%; PP: 97.4%, respectively), without de novo/worsening anemia. In conclusion, in a real-life study centered on genotype 2 patients with well-compensated cirrhosis, sofosbuvir-based regimens were associated with good SVR and tolerability rates, regardless of previous antiviral treatments, without a significant impact of on treatment ribavirin dose reductions.

## KEYWORDS

anemia, cirrhosis, hepatitis C, ribavirin, sofosbuvir

**Abbreviations:** AE, adverse events; DAA, direct-acting antiviral agents; DCV, daclatasvir; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4; GT, genotype; HCV, hepatitis C virus; ITPA, inosine triphosphatase; ITT, intention-to-treat; MELD, Model For End-Stage Liver Disease; PEG-IFN, pegylated interferon; PP, per-protocol; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; SVR12, undetectable HCV RNA at 12 weeks after therapy end; TE, treatment-experienced; TN, treatment-naïve.

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## 1 | INTRODUCTION

Hepatitis C is one of the most common causes of chronic liver disease, with >185 million infected subjects and nearly 400,000 deaths per year in the world.<sup>1</sup> In Europe, Italy is one of the countries with the greatest burden of hepatitis C virus (HCV) infection among the general population and has one of the highest mortality rates from HCV-related cirrhosis and hepatocellular carcinoma. The prevalence of infection is approximately 1%, though a rate as high as 7% has been reported among persons born between 1935 and 1944; generally, prevalence is lowest among persons aged 30 or less without apparent risk factors.<sup>2</sup>

Sofosbuvir (SOF), combined with ribavirin (RBV), has been widely used to treat genotype (GT) 2 HCV infection.<sup>3–8</sup> Although newer pangenotypic direct-acting antiviral agents (DAA) such as sofosbuvir plus velpatasvir and glecaprevir plus pibrentasvir have now emerged,<sup>9</sup> SOF plus RBV was the only approved therapy for Italian GT2 subjects until May 2017, and continued to be used at a lesser extent even afterwards. With regard to GT2, phase 3 trials showed very promising sustained virological response (SVR) rates for this regimen, but with lower performances—as low as 60%—in cirrhotic subjects, especially if treatment-experienced (TE).<sup>10</sup>

Moreover, concomitant administration of RBV typically resulted in common adverse events (AE), of which the most relevant is undoubtedly anemia. In the pegylated interferon (PEG-IFN)-era, RBV-induced anemia was reported with a varying incidence of 35.3% to 52.2% in Caucasian and Asian patients, respectively.<sup>11,12</sup> However, the individual effect of RBV dosage on the anemia development could not be properly investigated because of the concomitant bone marrow suppression caused by PEG-IFN. In the present DAA era, the role of RBV dose on SVR and anemia development can be better analyzed, but comprehensive researches on RBV dose modifications are mainly restricted, to the best of our knowledge, to Asian patients. Limiting to the most recent evidence, RBV dosage reduction occurred more frequently at dosages >15 mg/kg/day<sup>13</sup> but was generally not a determinant of a lower SVR.<sup>10</sup> In all studies, RBV-induced anemia was described as the most common AE, occurring in 15%–40% of subjects, with higher prevalences in patients ≥70 years, with liver cirrhosis, or with female gender. In any case, severe forms of anemia with consequent treatment discontinuations were reported only in a small proportion of patients.<sup>10,13–16</sup>

However, taking into consideration that anemia can represent a relevant problem especially for the most frail categories of subjects and that there are patients who are not eligible for RBV mostly due to baseline anemia, an alternative strategy to reducing RBV on treatment is represented by RBV-free DAA regimens, the first of which historically available was the association of SOF plus the NS5A inhibitor daclatasvir (DCV). This regimen is obviously burdened with fewer side effects, but the optimal duration of treatment in GT2 is still object of debate.<sup>16–18</sup>

An important further consideration is that the reported percentage of cirrhotic subjects in the aforementioned studies was quite modest (between 20% and 30%),<sup>10,13–18</sup> like almost all the previous ones, starting from clinical trials.<sup>19–22</sup> So, in our opinion, the current literature is

still not conclusive for the very specific subset of cirrhotic GT2 patients in defining the optimal RBV dose and the correct therapy duration, the latter one concerning specifically SOF plus RBV treatment, for which Italian (and European) clinicians could lawfully—in accordance with the guidelines available at that time—administer four different treatment schedules, namely 12, 16, 20, or 24 weeks.<sup>3–6</sup>

Therefore, in the present study we decided to share our experience and to analyze the efficacy and safety of SOF-based treatment regimens, and the consequences of RBV dosing modifications, for HCV GT2 infected cirrhotic subjects in a real-world scenario in Italy.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

We conducted a retrospective analysis on all the consecutive HCV mono-infected GT2 cirrhotic patients with native livers who received at least one dose of SOF-based therapy between January 2015 and April 2017 in one of eight tertiary hospitals in Italy. All persons had given their informed consent to the processing of personal data before starting antiviral treatments. The study protocol was approved by a centralized institutional review board (Comitato Etico Interaziendale Novara, Novara, Italy, IRB code CE 34/17) for all hospitals, and was therefore performed in accordance with the ethical standards set up in the Declaration of Helsinki 7th revision (2013). Any detail that might disclose the identity of the subjects under the study was carefully omitted. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Chronic hepatitis C was defined as the presence of HCV RNA for longer than 6 months. Cirrhosis diagnosis was based on histology or the presence of two or more of the following criteria: (a) nodularity, ascites or portal hypertension by imaging; (b) platelet count <140 × 10<sup>9</sup>/L; (c) varices by endoscopy; (d) liver stiffness ≥14 kPa by elastography (FibroScan).

From a total pool of 2765 patients, we enrolled 273 subjects, 194 treated with SOF (Sovaldi, Gilead Sciences)/RBV, and 79 with SOF/DCV (Daklinza, Bristol Myers Squibb). SOF was administered orally at a dose of 400 mg once daily, and DCV orally too at a dose of 60 mg once daily. SOF plus DCV arm was RBV-free, because it was authorized in Italy only for GT2 cirrhotic patients who were RBV intolerant or ineligible.<sup>17</sup> RBV starting dosages and any dose changes decided during treatment were as previously described by others, and always in accordance with the label.<sup>10,23</sup> Patients who received previous PEG-IFN or (other than SOF) DAA treatments for at least one dose were considered TE.

### 2.2 | Measurements for treatment response and adverse events of antiviral therapy

HCV RNA levels were measured in all study sites using ABBOTT RealTime HCV assay with a lower limit of quantitation of 12 IU/ml

and a lower limit of detection of 10 IU/ml (Abbott Laboratories). High viral load was defined as HCV RNA >6,000,000 IU/ml. Treatment responses were classified in accordance with the HCV guidelines by the European Association for the Study of the Liver.<sup>5</sup> SVR was defined as undetectable HCV RNA at 12 weeks after therapy end (SVR12). Viral breakthrough and relapse were categorized according to commonly accepted definitions.<sup>10</sup>

AE were based on review of medical records by the treating physicians. Anemia was defined according to World Health Organization criteria, and renal function following National Kidney Foundation guidelines.<sup>24,25</sup> The severity of on-treatment anemia was graded according to the National Cancer Institute Common Toxicity Criteria.<sup>26</sup>

## 2.3 | Statistical analysis

For descriptive statistics, continuous variables were expressed as medians and ranges, and categorical variables as frequencies and percentages. All data were assessed for normality using a Shapiro–Wilk test. The Mann–Whitney, Wilcoxon, and Kruskal–Wallis tests were used to compare continuous non parametric variables, as appropriate. Student's *t* test was used to compare means with a normal distribution. Pearson's chi-squared test was used to determine whether there was a significant difference between the expected and the observed frequencies in one or more categories. When sample sizes were small, Fisher's exact test was preferred in the analysis of contingency tables. A *p* value of <.05 was considered to be significant. All analyses were performed using Statistica 10.0 statistical software (Statsoft).

## 2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,<sup>27</sup> and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.<sup>28</sup>

# 3 | RESULTS

## 3.1 | Patients treated with sofosbuvir plus ribavirin

### 3.1.1 | Baseline patient characteristics with emphasis on ribavirin starting doses

The main baseline characteristics of SOF plus RBV treated patients (*n* = 194) are presented in Table 1 panel A. All individuals except two were Caucasian. Ten subjects (4 M, 6 F) were both anemic and with estimated glomerular filtration rate (eGFR) <60 ml/min.

According to patient grouping by weight, the initial median daily dosages of RBV were 1000 mg (<75 kg) and 1200 mg (≥75 kg), in

accordance with SOF data sheet.<sup>16</sup> However, only 106 (54.6%) subjects started the exact RBV daily dosage as recommended. More in detail, the initial doses of RBV (mg/day) were as follows (*n* of patients, %): 600 mg (5, 2.6%), 800 mg (41, 21.1%), 1000 mg (110, 56.7%), 1200 mg (36, 18.6%), and 1400 mg (2, 1.0%). When normalizing RBV to patient weight, initial median daily RBV dosage (13.9 mg/kg) was higher in patients <75 kg (*n* = 115, 14.3 mg/kg) than ≥75 kg (*n* = 69, 12.9 mg/kg) (*p* < .002). Body weight was significantly different between subjects started with lower and higher RBV doses, as expected for the previous considerations on the label: median values (range) were 58 (50–72) kg in patients with RBV doses of 800 mg/day and 90 (75–119) kg in those with RBV doses of 1200 mg/day (*p* < .001). The results were confirmed when comparing subjects with RBV doses of ≤800 mg/day, 1000 mg/day, and ≥1200 mg/day [58 (50–72), 72 (43–97), and 91 (75–126) kg, respectively; *p* < .001]. Applying the same methods, also the Model For End-Stage Liver Disease (MELD) was significantly different between lower and higher RBV dose users [respectively: 6.0 (5.0–13.0) vs. 8.0 (6.0–13.0), *p* = .01; 6.0 (5.0–13.0) vs. 7.0 (6.0–11.0) vs. 7.5 (6.0–13.0), *p* = .006]. Using a similar methodology to test whether other relevant baseline clinical and demographic factors were originated from the same distribution according to RBV dosing, no significant differences could be found for what concerns age (*p* = .226 and .308, respectively), Child score (*p* = .096 and .171, respectively), liver stiffness (*p* = .271 and .535, respectively), fibrosis-4 (FIB-4) index (*p* = .920 and .972, respectively), hemoglobin level (*p* = .322 and .578, respectively), platelet count (*p* = .379 and .306, respectively), creatinine (*p* = .818 and .946, respectively), and eGFR (*p* = .589 and .215, respectively). Finally, RBV starting doses as previously defined (i.e., 800 vs. 1200 mg/day, and ≤800 vs. 1000 vs. ≥1200 mg/day) were significantly different according to the following categorical variables represented as frequencies (percentages): male sex [respectively: 15/41 (36.6) vs. 28/36 (77.8), *p* < .001; 15/46 (32.6) vs. 49/110 (44.5) vs. 30/38 (78.9), *p* < .001] and PEG-IFN treatment-naïve (TN) status [respectively: 28/41 (68.3) vs. 10/36 (27.8), *p* < .001; 33/46 (71.7) vs. 84/110 (76.4) vs. 12/38 (31.6), *p* < .001].

### 3.1.2 | Treatment outcomes

Globally, SVR rates were not significantly different between intention-to-treat (ITT) (94.8%) and per-protocol (PP) (96.3%) analyses; similarly, no differences were found when considering TN (*n* = 129; ITT: 93.8%, PP: 95.3%, *p* = .500) or TE patients (*n* = 65; ITT: 96.9%, PP: 98.4%, *p* = .427). Moreover, similarly to previous experiences,<sup>10</sup> the subjects treated with a reduced RBV dose according to the decision of the attending physician showed similar SVR rates to those treated with the weight-based dose (ITT: 95.4% and 94.3%, *p* = 1.000; PP: 97.7% and 95.2%, *p* = .461, respectively). The efficacies were also not significantly different between those weighted <75 and ≥75 kg, both in ITT (96.6% and 92.0%, respectively; *p* = .189) and PP (97.4% and 96.5%, respectively; *p* = .431) analyses.

	(A) SOF plus RBV (n = 194)	(B) SOF plus DCV (n = 79)	(C) p value
Male sex, n	94 (48.4)	32 (40.5)	.284
Age, years	74 (42–87)	68 (36–80)	<b>&lt;.001</b>
Body mass index, kg/m <sup>2</sup>	25.3 (17.1–40.1)	24.9 (18.2–31.2)	.201
HCV RNA, ×10 <sup>3</sup> IU/ml	865 (9–85, 200)	1608 (26–16, 100)	<b>.007</b>
High viral load <sup>a</sup> , n	13 (6.7%)	11 (13.9)	.063
Child–Pugh score	5 (5–8)	5 (5–7)	.694
Child–Pugh class, n for A, B	182 (93.8), 12 (6.2)	76 (96.2), 3 (3.8)	.565
MELD score	7 (5–13)	7 (6–15)	.901
Basal transient elastography, kPa	18.2 (10.1–75.0) <sup>b</sup>	17.1 (12.1–53.1) <sup>c</sup>	.092
ALT, IU/L	64 (12–321)	50 (21–201)	.102
Total bilirubin, mg/dl	0.9 (0.4–2.0)	0.8 (0.3–1.8)	.346
International normalized ratio, Units	1.1 (0.8–1.6)	1.0 (0.9–1.5)	.803
Platelets, ×10 <sup>9</sup> /L	135 (33–331)	111 (38–201)	<b>.011</b>
Creatinine, mg/dl	0.69 (0.43–1.4)	0.8 (0.5–2.1)	.932
eGFR <sup>d</sup> , ml/min	74 (46–146)	62 (31–101)	.104
Stage of renal function, n for 1, 2, 3 <sup>e</sup>	45 (23.2), 95 (49.0), 54 (27.8)	16 (20.3), 43 (54.4), 20 (25.3)	.738
Albumin, g/dl	3.8 (2.8–4.6)	3.7 (2.8–4.5)	.604
Hemoglobin, g/dl	13.1 (9.1–17.1)	11.2 (8.4–15.0)	<b>&lt;.001</b>
Baseline anemia, n	47 (24.2)	39 (49.4)	<b>&lt;.001</b>
Naïve/experienced to PEG-IFN treatment, n	129 (66.5), 65 (33.5)	37 (46.8), 42 (53.2)	<b>.002</b>
FIB-4 index	4.4 (1.2–38.9)	3.4 (2.2–19.1)	.055
FIB-4 index, n for <1.45, 1.45–3.25, >3.25	6 (3.1), 51 (26.3), 137 (70.6)	3 (3.8), 25 (31.6), 51 (64.6)	.635

Note:: Panel A: Sofosbuvir plus ribavirin treatments. Panel B: Sofosbuvir plus daclatasvir treatments; Panel C: Differences between the two treatments. Data are presented as median (range) for continuous variables, and as frequency (%) for categorical variables. Bold text indicates a statistically significant difference with a *p* value less than .05.

<sup>a</sup>Defined as HCV RNA >6,000,000 IU/ml.

<sup>b</sup>Available for 176 (90.7%) patients.

<sup>c</sup>Available for 73 (92.4%) patients.

<sup>d</sup>Estimated with CKD-EPI creatinine equation for persons between 18 and 70 years old, and with BIS 1 equation for subjects over 70 years of age.

<sup>e</sup>According to National Kidney Foundation guidelines.

### 3.1.3 | Adverse events

AE were observed in 142 patients (73.2%). The most relevant one was anemia (*n* = 88, 45.3%; mild: 34.5%, moderate: 7.7%, severe: 3.1%), with, as a consequence, the need for a (at least temporarily) dose reduction of RBV. The rates of on-treatment RBV-induced anemia were more frequent in patients with baseline anemia as previously defined [63.8% (30/47) vs. 39.4% (58/147), respectively; *p* = .004], baseline platelet level <100 × 10<sup>9</sup>/L [60.9% (39/64) vs. 36.6% (49/134), respectively; *p* = .003], chronic kidney disease grade ≥3 [63.0% (34/54) vs. 38.6% (54/140), respectively; *p* = .004], age >65 years [49.7% (76/153)

vs. 29.3% (12/41), respectively; *p* = .02], RBV dose >15 mg/kg [66.0% (35/53) vs. 37.6% (53/141), respectively; *p* < .001]. RBV-induced anemia was not prevalent in those weighing <75 kg [48.7% (58/119) vs. 40.0% (30/75), respectively; *p* = .240] or with female sex [47.0% (47/100) vs. 43.6% (41/94), respectively; *p* = .667].

Any-grade other more prevalent AE were fatigue (55.1%), headache (30.9%), nausea (26.3%), insomnia (17.5%), and rash (2.1%). However, only three patients (1.5%) prematurely discontinued antiviral therapy. In two cases this was due to non-fatal extrahepatic causes (one acute kidney injury and one stroke); the third patient died of rapidly progressive liver failure, but had already advanced

TABLE 1 Main baseline demographic and clinical features of the studied population

liver disease at the beginning of antiviral therapy (Child Pugh and MELD scores of 8 and 11, respectively).

### 3.1.4 | Treatment durations

Median duration of treatment—as programmed before starting therapy—was 16 weeks, which was not different from that which could be actually administered ( $p = .092$ ). However, the treatment schedules chosen varied amongst clinicians: 12 weeks ( $n = 2$ , 1%), 16 weeks ( $n = 99$ , 51%), 20 weeks ( $n = 64$ , 33%), and 24 weeks ( $n = 29$ , 15%), as allowed at that time.<sup>3–6</sup> So, we performed multiple comparative analyses between these treatment durations, to explore if there was a possible propension to treat longer the more severe subjects. In particular, when comparing the main patient demographic and clinical parameters between shorter (i.e., <20 weeks,  $n = 101$ ) and prolonged regimens (i.e.,  $\geq 20$  weeks,  $n = 93$ ), no significant differences could be found in median body mass index ( $p = .389$ ), HCV RNA ( $p = .280$ ), basal transient elastography ( $p = .152$ ), FIB-4 index ( $p = .368$ ), Child score ( $p = .141$ ), MELD score ( $p = .121$ ), platelet count ( $p = .582$ ), albumin ( $p = .703$ ), and creatinine ( $p = .741$ ). Similarly, no differences emerged in sex ( $p = .484$ ) distribution. The only relevant parameters which differed between the two groups were median hemoglobin [13.9 (9.2–17.1) vs. 12.4 (11.0–16.4) g/dl, respectively;  $p = .024$ ] and the frequency of TE subjects [44.5% vs. 21.5%, respectively;  $p < .001$ ]. In any case, the duration of therapy—as previously categorized—was not statistically associated with SVR, both in ITT (94.1% and 95.7%, respectively;  $p = .750$ ) and PP (96.0% and 96.7%, respectively;  $p = 1.000$ ) analyses.

## 3.2 | Patients treated with sofosbuvir plus daclatasvir

### 3.2.1 | Baseline patient characteristics

The main baseline characteristics of SOF plus DCV treated patients ( $n = 79$ ) are presented in Table 1 panel B. All individuals were Caucasian. Six subjects (3 M, 3 F) were both anemic and with eGFR <60 ml/min.

As previously mentioned, this was a RBV-free treatment, because it was authorized in Italy—as an off-label indication—only for cirrhotic patients who were intolerant to RBV in previous treatments ( $N = 40$ ) or ineligible for RBV due to significant baseline anemia ( $N = 39$ ).<sup>17</sup> Of the latter group, two subjects were TE.

### 3.2.2 | Treatment outcomes and adverse events

According to local reimbursement criteria, all patients were treated with the same treatment duration (i.e., for 12 weeks), and the SVR rates were 96.2% (ITT) and 97.4% (PP), without significant

differences between TN and TE patients (ITT: 94.6% and 97.6%,  $p = .597$ ; PP: 97.2% and 97.6%,  $p = 1.000$ , respectively). The most common reported (mild) AE were headache (7.6%), dyspepsia (6.3%), and nausea (5.1%); no patient experienced significant de-novo or worsening of pre-existing anemia. Only one subject prematurely discontinued therapy due to an acute myocardial infarction, while all the other ones could complete their planned schedule.

## 3.3 | Comparison between the two treatment groups

Although this was not a randomized trial, the two treated populations (i.e., SOF plus RBV,  $n = 194$ ; SOF plus DCV,  $n = 79$ ) showed a posteriori no relevant clinical diversity in the main patient characteristics and demographics (Table 1, panel C), not taking into account the expected higher prevalence of TE or baseline anemic subjects in the SOF plus DCV arm due to the initial prescription indications. More in detail, the severity of liver disease was comparable between the two therapeutic regimens; the only minor differences were found in median age, HCV viral load, and platelet count.

## 4 | DISCUSSION

Our analysis confirmed previous recent reports on high real-life efficacy and sufficient tolerability of SOF plus RBV therapy for HCV GT2 patients with well-compensated cirrhosis.<sup>10,13–16,29–37</sup> The same considerations can be made for DCV-based regimens, though resulting less studied in the recent literature.<sup>10,16,34,36–39</sup> However, some important issues have to be addressed. First of all, the aforementioned studies, although providing a detailed overview of the performance of these treatment regimens, did not focus, like also almost all the other ones available in the previous literature, on the very specific subset of patients with cirrhosis, which remains, in our opinion, with unresolved issues. As a matter of fact, in all the above-cited researches, only a minority of patients (generally ranging from 20% to 45%) had a diagnosis of cirrhosis. Our study, on the contrary, was centered only on patients with confirmed cirrhosis. Secondly, most of the recent researches studied Asian populations (mainly Far East),<sup>10,13–16,29,31,33,34,39–44</sup> so Caucasian patients were not extensively analyzed.<sup>17,30,45–47</sup> Instead, in our case series all subjects were Caucasian. This is relevant, as GT2 has a major prevalence ( $\geq 10\%$ ) also for what concerns this ethnicity, mainly in Western Europe (where the present study was conducted) and white North Americans.<sup>1,48</sup> Finally, an explanation why—in contrast to the situation we detailed in our real-life study—SOF plus DCV represented only a minority of the total reported prescriptions for the GT2 subpopulation, probably lies not only in different national prescribing policies but above all in the fact that, again, ours was a casuistry entirely of cirrhotic subjects (thus making this RBV-free treatment preferable in the most frail patients because potentially burdened by fewer side effects).

Another key point that differentiates, in our view, our study is that RBV detailed prescription was not analyzed in detail in most previous researches. This, probably, is due to the fact that available guidelines recommended a fixed dosage of 1200 mg/day for patients  $\geq 75$  kg and 1000 mg/day for those  $< 75$  kg.<sup>3–6</sup> Nevertheless, our study revealed that about 1/5 of the prescribers initiated RBV at 800 mg/day, possibly based on their previous experience with PEG-IFN. In addition, the weight-based dosages had to be adjusted throughout therapy in 45.4% of cases. The pathophysiological mechanism for this resides in hemolysis, which is a common side effect of RBV and the major reason for its dose reduction. Age, baseline hemoglobin and platelet levels, chronic kidney disease, and RBV dose have all been reported to contribute to this RBV-induced anemia and consequent dose reduction, as confirmed in our casuistry.<sup>49,50</sup> More in detail, for what concerns Caucasian patients, anemia caused by RBV was frequently reported (around 35%) in the era of PEG-IFN and RBV combination therapies, with even higher incidences in cirrhotic subjects (about 70%).<sup>12,51,52</sup> Similar reports were also made in Asian patients.<sup>53,54</sup> Most of these studies were related to inosine triphosphatase (ITPA) polymorphisms.<sup>55</sup> As a consequence of drug-induced anemia, the recorded RBV dose reduction rates were quite substantial (generally more than 33%), again with higher frequencies in the subjects with more advanced disease.<sup>53</sup> The same report that ITPA polymorphisms are implicated in RBV-induced anemia was subsequently provided also with regard to SOF/RBV combination therapies, as in the case of the present study, without evidence of association with the clinical outcome.<sup>56</sup>

With regard to the latter point, our data, although not including a genetic analysis, provided indirect evidence in favor, since the SVR rate in individuals who were given a reduced RBV dose was not lower than in those treated with the standard weight-based dose, similarly to previous reports in Asian subjects.<sup>10</sup> Moreover, no differences amongst SVR rates could be found between subjects weighted  $< 75$  and  $\geq 75$  kg, and the same occurred when the patients were further stratified according to all different RBV dosages (data not shown). Therefore, the significant reduction in RBV dosing likely yielded improved treatment compliance and consequent SVR. In ultimate end, this study confirmed that RBV may still have a role in the therapy of HCV patients for its added value to achieve SVR in combination with a SOF monotherapy. We could also speculate that, as suggested by others, in this cohort of subjects with compensated cirrhosis RBV contributed to the shortening of therapy, with acceptable side effects in most cases and without loss of efficacy or real treatment disruption urgencies.<sup>57</sup> However, larger multicenter trials are mandated for better configuration of final decisions on which exact doses are required for such patients on an individual basis, beyond the previously reported fixed start doses based merely on body weight. In this respect, RBV steady-state plasma levels would seem promising for both predicting SVR and preventing significant anemia, and may be used as a tool in addition to simple RBV toxicity monitoring for a more rational average drug dose adjusting in the case of patients with difficult-to-cure characteristics such as impaired renal function and/or cirrhosis.<sup>58</sup> In this regard, it must be said that most published

studies showed contradictory results, possibly due to their small sample sizes and retrospective nature; it should also be noted that none of these studies was focused on cirrhotic patients.<sup>59–62</sup> Among other things, this methodology—as well as the systematic baseline research at the ITPA genotype—remains currently the prerogative of a few research laboratories and would be difficult to use in clinical practice, also taking into account that these are outpatient patients.

A further noteworthy consideration with regard to RBV use—and that at least partially could question the above considerations—is that, at least in our experience, there may have been a possible bias in favor of the efficacy of the RBV reducing strategy due to the fact that the most frail subjects (in particular those with contraindications to the use of RBV) were offered an alternative all-oral therapy based on SOF and DCV. This may have allowed the treatment (and consequent cure) of subjects that otherwise would likely have experienced an even higher incidence of RBV-related complications, primarily anemia, with the need for significant RBV dose reductions—or even full discontinuation—and consequent potential lower viral eradication rates. Obviously, being the SOF/DCV arm RBV-free, anemia was not a documented side effect in that subpopulation.

For what concerns SVR rates of SOF plus RBV treatments, they were very convincing, and even slightly higher than most clinical trial and real-life records. These results were obtained regardless of previous antiviral treatments, reduced RBV dosing (taking into account all the above considerations) and treatment duration (provided it was  $> 12$  weeks). As regarding the latter point, an interesting remark is that the 12 week schedule, representing initially the most widely studied regimen, was adopted in our local experience only by a small minority (1%) of clinicians, probably because they feared a possible suboptimal efficacy in patients with advanced fibrosis. As a matter of fact, the main five phase III SOF clinical trials (known as the FISSION, POSITRON, FUSION, VALENCE, and BOSON trials)—none of which, however, was focused specifically on the subpopulation of HCV GT2-infected cirrhotic patients—globally showed average SVR12 rates around 83% for the 12 week schedule (investigated in 49 of the 90 cirrhotic GT2 subjects collectively studied).<sup>19–22</sup> The same trials suggested that the 12 week schedule—despite having many advantages—was suboptimal in the cirrhotic setting, and that more prolonged durations (i.e., 16 and 24 weeks) were associated to higher SVR rates (up to 100% in TN subjects). This evidence was further confirmed in the much more numerous real-life studies that subsequently became available.<sup>14–16,29,45,46,63</sup> Coming back to our study, it is also noteworthy that the second choice in order of preference (51%) was 20 weeks (similarly to what happened in other European countries), although, for what concerns GT2 cirrhotic subjects, it was not formally tested in the aforementioned clinical trials, but—to the best of our knowledge—in only one major clinical study.<sup>30</sup> So, in our opinion, the best possible therapy duration for this very specific subset of patients (i.e., 16, 20, or 24 weeks) remains not completely defined in the available clinical literature and should probably deserve some more additional research. In any case, at least in our

casuistry, we could not demonstrate a possible propensity to treat the more severe subjects with a longer duration (i.e.,  $\geq 20$  weeks). This may be due also to the fact that our case series was very homogeneous, that is, it consisted only of cirrhotic patients, in the vast majority compensated (94% Child A, only 6% Child B, no Child C subjects).

Moreover, the most common AE of SOF/RBV, including anemia which has been discussed above, were similar to other reports, and in any case they were generally mild/moderate.<sup>47,64,65</sup> Incidentally, all the few dropouts were attributable to reasons not related to the prescribed therapy. We also consider the safety data of particular significance since this was a frail mostly elderly population, like typical cohorts of cirrhotic patients in the Western world.<sup>52,66-68</sup>

However, this research reveals also many possible shortcomings. First, the frequency and severity of AE were estimated on the basis of clinical charts and may partially have been classified in an inaccurate way due to the different individual tolerance. Nonetheless, the most relevant occurrence (i.e., anemia) did not lead to treatment discontinuations. Second, the rationale for the RBV dose choice was not formally explored as this was a retrospective study. In any case, what emerged is that higher RBV doses were generally related to higher body weight (obviously, the main determinant of RBV dosage), male sex, higher MELD score and TE status. Other well-known predictive factors of RBV-induced anemia—such as advanced age, lower baseline hemoglobin values, and impaired renal function—were not correlated with the starting dose of RBV. This may suggest that RBV dosing was not primarily based on the patient predicted tolerability and concomitant diseases—as in the PEG-IFN era—and that the clinicians preferred to follow as closely as possible the label indications, especially in those subjects with unfavorable predictors of SVR (such as previous treatment failure or more severe liver damage), probably taking into account that this advanced fibrosis-population had a lower probability of response. From this point of view it is paradigmatic that this clinical approach was not a prerogative only of experienced physicians, as no significant differences in initial RBV dosage were observed between clinicians with work experience greater or less than 10 years ( $p = .437$ , data not shown).

In conclusion, SOF-based therapies proved to be highly effective and tolerable in a big cohort of Italian cirrhotic patients with GT2 HCV infection, regardless of past antiviral experience and current treatment duration (provided it was longer than 12 weeks). Moreover, a low RBV dosage was as effective as the standard dose, confirming previous Asian experiences.<sup>10,13-16,33,44,50</sup>

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## DISCLOSURE

All authors declare they have no financial support or relationships that may pose conflict of interest.

## ETHICS STATEMENT

The study protocol was approved by a centralized institutional review board (Comitato Etico Interaziendale Novara, Novara, Italy, IRB code CE 34/17) for all hospitals, and was therefore performed in accordance with the ethical standards set up in the Declaration of Helsinki 7th revision (2013).

## PATIENT CONSENT STATEMENT

All persons had given their informed consent to the processing of personal data before starting antiviral treatments.

## PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

N/A.

## CLINICAL TRIAL REGISTRATION

N/A.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## REFERENCES

- Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology*. 2015;61:77-87.
- Andriulli A, Stroffolini T, Mariano A, et al. Declining prevalence and increasing awareness of HCV infection in Italy: a population-based survey in five metropolitan areas. *Eur J Intern Med*. 2018;53:79-84.
- AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology*. 2015;62:932-954.
- Pawlotsky JM, Aghemo A, Back D, et al. EASL recommendations on treatment of hepatitis C 2015. *J Hepatol*. 2015;63:199-236.
- Omata M, Kanda T, Wei L, et al. APASL consensus statements and recommendation on treatment of hepatitis C. *Hepatol Int*. 2016;10:702-726.
- Italian Association for the Study of the Liver (AISF). AISF guidance document for the rational use of second-generation direct antiviral agents in the categories of patients affected from chronic hepatitis C and eligible for reimbursement in Italy. [http://www.clubepatol.org/ogiospedalieri.it/wp-content/uploads/2017/01/Linee-guida-AISF-2015\\_05\\_26.pdf](http://www.clubepatol.org/ogiospedalieri.it/wp-content/uploads/2017/01/Linee-guida-AISF-2015_05_26.pdf). Accessed March 29, 2021.
- Chinese Society of Hepatology, Chinese Medical Association, Wei L; Chinese Society of Infectious Diseases, Chinese Medical Association, Hou JL. The guideline of prevention and treatment for hepatitis C: a 2015 update. *Zhonghua Gan Zang Bing Za Zhi*. 2015;2015(23):906-923.
- Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines management of hepatitis C: treatment of chronic hepatitis C. *Clin Mol Hepatol*. 2017;2018(24):169-229.

9. AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. *Clin Infect Dis*. 2018;67:1477-1492.
10. Jang ES, Kim K-A, Kim YS, et al. Real-life effectiveness and safety of sofosbuvir-based therapy in genotype 2 chronic hepatitis C patients in South Korea, with emphasis on the ribavirin dose. *Gut Liv*. 2020;14:775-782.
11. Kwon JH, Bae SH, Choi JY, et al. Assessment of the efficacy of reducing peginterferon alpha-2a and ribavirin dose on virologic response in Koreans with chronic hepatitis C. *Korean J Intern Med*. 2009;24:203-211.
12. D'Avolio A, Ciancio A, Siccardi M, et al. Inosine triphosphatase polymorphisms and ribavirin pharmacokinetics as determinants of ribavirin-associate anemia in patients receiving standard anti-HCV treatment. *Ther Drug Monit*. 2012;34:165-170.
13. Yoon JH, Jun CH, Seo JH, et al. Sofosbuvir plus ribavirin for the treatment of hepatitis C virus genotype 2 in Korea: what's the optimal dosage of ribavirin in real-world setting? *J Dig Dis*. 2019;20:31-37.
14. Kim YM, Kim SB, Song IH, et al. Efficacy and safety of sofosbuvir plus ribavirin for Korean patients with hepatitis C virus genotype 2 infection: a retrospective multi-institutional study. *Clin Mol Hepatol*. 2018;24:311-318.
15. Han SY, Woo HY, Heo J, et al. The predictors of sustained virological response with sofosbuvir and ribavirin in patients with chronic hepatitis C genotype 2. *Korean J Intern Med*. 2021;36(3):544-556. <https://doi.org/10.3904/kjim.2018.329>
16. Tsai WL, Wang CF, Cheng JS, Chen WC, Bair MJ, Lo CC. Sofosbuvir-based regimen for genotype 2 HCV infected patients in Taiwan: a real world experience. *PLoS One*. 2020;15:e0227424.
17. Mangia A, Arleo A, Copetti M, et al. The combination of daclatasvir and sofosbuvir for curing genotype 2 patients who cannot tolerate ribavirin. *Liver Int*. 2016;36:971-976.
18. Kurniawan J, Gani RA, Hasan I, et al. Comparative efficacy of sofosbuvir-ribavirin versus sofosbuvir-daclatasvir for treatment of chronic hepatitis C in an area with limited NS5A inhibitor availability. *Indian J Gastroenterol*. 2018;37:520-525.
19. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368:1867-1877.
20. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368:1878-1887.
21. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med*. 2014;370:1993-2001.
22. Foster GR, Pianko S, Brown A, et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. *Gastroenterology*. 2015;149:1462-1470.
23. European Medicines Agency (EMA). Annex I - Summary of product characteristics. In: *Sovaldi: European public assessment report (EPAR) - Product Information*. [https://www.ema.europa.eu/en/documents/product-information/sovaldi-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/sovaldi-epar-product-information_en.pdf). Accessed March 31, 2021.
24. World Health Organization. (WHO). Defining anaemia. In: *WHO Global Database on Anaemia. Worldwide Prevalence of Anemia 1993-2005*. [https://apps.who.int/iris/bitstream/handle/10665/43894/9789241596657\\_eng.pdf;sequence=1](https://apps.who.int/iris/bitstream/handle/10665/43894/9789241596657_eng.pdf;sequence=1). Accessed March 30, 2021.
25. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39:S1-S266.
26. Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: version 2.0. An improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;47:13-47.
27. Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucleic Acids Res*. 2018;46(D1):D1091-D1106. <https://doi.org/10.1093/nar/gkx1121>
28. Alexander SPH, Fabbro D, Kelly E, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: enzymes. *Br J Pharmacol*. 2019;176(Suppl 1):S297-S396. <https://doi.org/10.1111/bph.14752>
29. Seo HY, Seo MS, Yoon SY, Choi JW, Ko SY. Full-dose sofosbuvir plus low-dose ribavirin for hepatitis C virus genotype 2-infected patients on hemodialysis. *Korean J Intern Med*. 2020;35:559-565.
30. Mangia A, Susser S, Piazzolla V, et al. Sofosbuvir and ribavirin for genotype 2 HCV infected patients with cirrhosis: a real life experience. *J Hepatol*. 2017;66:711-717.
31. Nozaki A, Chuma M, Hara K, et al. Sofosbuvir-based therapies associated with regression of liver fibrosis in patients with hepatitis C virus infection: a prospective observational study. *Medicine (Baltimore)*. 2021;100:e25110.
32. Choi IS, Kim KM, Shim SG. Combination treatment with sofosbuvir and ribavirin for patients diagnosed with hepatitis C genotype 2: a real-world, single-center study. *Arab J Gastroenterol*. 2021;22:23-27.
33. Akahane T, Kurosaki M, Itakura J, et al. Real-world efficacy and safety of sofosbuvir + ribavirin for hepatitis C genotype 2: a nationwide multicenter study by the Japanese Red Cross Liver Study Group. *Hepatol Res*. 2019;49:264-270.
34. Cheng T-S, Liang P-C, Huang C-F, et al. Real-world effectiveness of direct-acting antiviral agents for chronic hepatitis C patients with genotype-2 infection after completed treatment. *Kaohsiung J Med Sci*. 2021;37:334-345.
35. Tsertsvadze T, Gamkrelidze A, Nasrullah M, et al. Treatment outcomes of patients with chronic hepatitis C receiving sofosbuvir-based combination therapy within national hepatitis C elimination program in the country of Georgia. *BMC Infect Dis*. 2020;20:30.
36. Lédinghen V, Lusivika-Nzinga C, Bronowicki J-P, et al. Sofosbuvir-Daclatasvir is suboptimal in patients with genotype 2 chronic hepatitis C infection: real-life experience from the HEPATHER ANRS CO22 cohort. *J Viral Hepat*. 2020;27:964-973.
37. Liu C-H, Su T-H, Liu C-J, et al. Sofosbuvir-based direct acting antiviral therapies for patients with hepatitis C virus genotype 2 infection. *J Gastroenterol Hepatol*. 2019;34:1620-1625.
38. Miotto N, Mendes LC, Zanaga LP, et al. All-oral direct antiviral treatment for hepatitis C chronic infection in a real-life cohort: the role of cirrhosis and comorbidities in treatment response. *PLoS One*. 2018;13:e0199941.
39. Wu S-H, Chu C-J, Su C-W, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, is highly effective for all kinds of genotype-2 chronic hepatitis-C infection in Taiwan. *J Chin Med Assoc*. 2019;82:693-698.
40. Chen C-Y, Huang C-F, Cheng P-N, et al. Factors associated with treatment failure of direct-acting antivirals for chronic hepatitis C: a real-world nationwide hepatitis C virus registry programme in Taiwan. *Liver Int*. 2021;41(6):1265-1277. <https://doi.org/10.1111/liv.14849>
41. Yang Y, Wu F-P, Wang W-J, et al. Real life efficacy and safety of direct-acting antiviral therapy for treatment of patients infected with hepatitis C virus genotypes 1, 2 and 3 in northwest China. *World J Gastroenterol*. 2019;25:6551-6560.
42. Cheng PN, Chiu YC, Chien SC, Chiu HC. Real-world effectiveness and safety of sofosbuvir plus daclatasvir with or without ribavirin for genotype 2 chronic hepatitis C in Taiwan. *J Formos Med Assoc*. 2019;118:907-913.
43. Sho T, Suda G, Nagasaka A, et al. Safety and efficacy of sofosbuvir and ribavirin for genotype 2 hepatitis C Japanese patients with renal dysfunction. *Hepatol Res*. 2018;48:529-538.
44. Ohya K, Akuta N, Suzuki F, et al. Predictors of treatment efficacy and liver stiffness changes following therapy with Sofosbuvir plus



- Ribavirin in patients infected with HCV genotype 2. *J Med Virol*. 2018;90:919-925.
45. Louie V, Latt NL, Gharibian D, et al. Real-world experiences with a direct-acting antiviral agent for patients with hepatitis C virus infection. *Perm J*. 2017;21:16-096.
  46. Kondili LA, Gaeta GB, Brunetto MR, et al. Incidence of DAA failure and the clinical impact of retreatment in real-life patients treated in the advanced stage of liver disease: interim evaluations from the PITER network. *PLoS One*. 2017;12:e0185728.
  47. Welzel TM, Nelson DR, Morelli G, et al. Effectiveness and safety of sofosbuvir plus ribavirin for the treatment of HCV genotype 2 infection: results of the real-world, clinical practice HCV-TARGET study. *Gut*. 2017;66:1844-1852.
  48. Manos MM, Shvachko VA, Murphy RC, Arduino JM, Shire NJ. Distribution of hepatitis C virus genotypes in a diverse US integrated health care population. *J Med Virol*. 2012;84:1744-1750.
  49. Ochi H, Maekawa T, Abe H, et al. ITPA polymorphism affects ribavirin-induced anemia and outcomes of therapy—a genome-wide study of Japanese HCV virus patients. *Gastroenterology*. 2010;139:1190-1197.
  50. Chen C-C, Tung S-Y, Wei K-L, et al. Incidence, risk factors and impact on virological response of anemia in chronic genotype 2 hepatitis C receiving sofosbuvir plus ribavirin. *J Formos Med Assoc*. 2020;119:532-537. <https://doi.org/10.1016/j.jfma.2019.07.028>
  51. Di Marco V, Calvaruso V, Grimaudo S, et al. Role of IL-28B and inosine triphosphatase polymorphisms in efficacy and safety of Peg-Interferon and ribavirin in chronic hepatitis C compensated cirrhosis with and without esophageal varices. *J Viral Hepat*. 2013;20:113-121.
  52. Parmar P, Shafran SD, Borgia SM, Doucette K, Cooper CL. Hepatitis C direct-acting antiviral outcomes in patients 75 years and older. *JGH Open*. 2020;5:253-257.
  53. Hu KQ, Freilich B, Brown RS, Brass C, Jacobson IM. Impact of Hispanic or Asian ethnicity on the treatment outcomes of chronic hepatitis C: results from the WIN-R trial. *J Clin Gastroenterol*. 2011;45:720-726.
  54. Chi X, Wang M, Pan YU, et al. Inosine triphosphate pyrophosphatase polymorphisms are predictors of anemia in Chinese patients with chronic hepatitis C during therapy with ribavirin and interferon. *J Gastroenterol Hepatol*. 2020;35:97-103.
  55. Fellay J, Thompson AJ, Ge D, et al. ITPA gene variants protect against anaemia in patients treated for chronic hepatitis C. *Nature*. 2010;464:405-408.
  56. Kozuka R, Hai H, Teranishi Y, et al. Correlation between polymorphism in the inosine triphosphatase and the reductions in hemoglobin concentration and ribavirin dose during sofosbuvir and ribavirin therapy. *J Gastroenterol Hepatol*. 2017;32:1495-1502.
  57. Alhaddad O, Wahb A, Sabry A, et al. Role of ribavirin in the era of direct-acting antiviral therapies of chronic hepatitis C. *Expert Rev Anti Infect Ther*. 2020;18:817-822.
  58. van Tilborg M, Lieveld FI, Smolders EJ, et al. Ribavirin steady-state plasma level is a predictor of sustained virological response in hepatitis C-infected patients treated with direct-acting antivirals. *Aliment Pharmacol Ther*. 2017;46:864-872.
  59. Martinello M, Schteinman A, Alavi M, et al. The impact of ribavirin plasma concentration on the efficacy of the interferon-sparing regimen, sofosbuvir and ribavirin. *Antivir Ther*. 2016;21:127-132.
  60. Kovari H, Rusmann S, Ledergerber B, et al. Ribavirin concentrations do not predict sustained virological response in HIV/HCV-coinfected patients treated with ribavirin and pegylated interferon in the Swiss HIV Cohort Study. *PLoS One*. 2015;10:e0133879.
  61. Kuntzen T, Kuhn S, Kuntzen D, Seifert B, Müllhaupt B, Geier A. Influence of ribavirin serum levels on outcome of antiviral treatment and anemia in hepatitis C virus infection. *PLoS One*. 2016;11:e0158512.
  62. Pedersen C, Alsö Å, Lagging M, et al. Ribavirin plasma concentration is a predictor of sustained virological response in patients treated for chronic hepatitis C virus genotype 2/3 infection. *J Viral Hepat*. 2011;18:245-251.
  63. Butt AA, Yan P, Shaikh OS, Chung RT, Sherman KE. Sofosbuvir-based regimens in clinical practice achieve SVR rates closer to clinical trials: results from ERCHIVES. *Liver Int*. 2016;36:651-658.
  64. Yang YM, Choi EJ. Efficacy and safety outcomes of sofosbuvir-based treatment regimens for hepatitis C virus-infected patients with or without cirrhosis from phase III clinical trials. *Ther Clin Risk Manag*. 2017;13:477-497.
  65. Chang CY, Nguyen P, Le AN, et al. Real-world experience with interferon-free, direct acting antiviral therapies in Asian Americans with chronic hepatitis C and advanced liver disease. *Medicine (Baltimore)*. 2017;96:e6128.
  66. Atsukawa M, Tsubota A, Kondo C, et al. Effectiveness and safety of community-based treatment with sofosbuvir plus ribavirin for elderly patients with genotype 2 chronic hepatitis C. *Dig Liver Dis*. 2017;49:1029-1035.
  67. Ogawa E, Furusyo N, Nomura H, et al. Effectiveness and safety of sofosbuvir plus ribavirin for HCV genotype 2 patients 65 and over with or without cirrhosis. *Antiviral Res*. 2016;136:37-44.
  68. Nishida N, Kono M, Minami T, et al. Safety, tolerability, and efficacy of sofosbuvir plus ribavirin in elderly patients infected with hepatitis C virus genotype 2. *Dig Dis*. 2016;34:632-639.

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