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# Efficacy and Safety of Sofosbuvir-containing Regimens in Chronic Hepatitis C Patients with Genotype 2 and 3: a Comprehensive Analysis of 18 Randomized Controlled Trials

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## ABSTRACT

**Background and Aim**: Sofosbuvir is a hepatitis C virus (HCV) NS5B polymerase inhibitor. The objective of this study was to explore the efficacy and safety of sofosbuvir for HCV genotype (GT) 2 and 3 infected patients.
**Method**: We searched randomized controlled trials (RCTs) which analyzed the efficacy and safety of sofosbuvir-containing regimens for HCV GT 2/3 infected patients and collected data. The endpoints were sustained virological response 12- and 24-weeks after the cessation of therapy (SVR12 and SVR24), the adverse events (AEs) and the severe adverse events (SAEs).
**Results**: Eighteen trials comprising 2,975 HCV GT 2/3 infected patients were included. The pooled estimate SVR12, SVR24, AEs and SAEs rates were 84.6% (95% CI: 83.2-86.0), 83.7% (95% CI: 82.0-85.2), 83.8 (95% CI: 82.3-85.3) and 3.9 (95% CI: 3.2-4.8). The SVR12 rate of sofosbuvir-containing regimens for HCV GT 2 infection was higher than that for HCV GT 3 infection (95.7% vs. 80.8%). The sofosbuvir combined with velpatasvir (with or without ribavirin) regimen presented a higher SVR12 rate and lower AEs rate than the sofosbuvir combined with ribavirin (with or without peg-IFN) regimen (94.9% vs. 80.7% for SVR12 rate; 69.3% vs. 87.7% for AEs rate).
**Conclusions**: The sofosbuvir-containing regimens in patients with HCV GT 2 infection have better efficacy than in patients with HCV GT 3 infection.

**Key words:** hepatitis C virus – sofosbuvir – sustained virological response – combination therapy.

**Abbreviations**: AE: adverse effect; CHC: chronic hepatitis C; DAA: direct-acting antiviral agent; FDC: Fixed Dose Combination; GT: genotype; HCV: hepatitis C virus; IL28B: interleukin 28B; LLOQ: lower limit of quantitation; Peg-IFN: Peg-interferon; RBV: ribavirin; P+R: peg-interferon alfa + ribavirin; RCT: randomized controlled trial; SAE: severe adverse effect; SVR: sustained virological response; S+D+(R): sofosbuvir + daclatasvir (with or without RBV); S+G+E: sofosbuvir + grazoprevir/elbasvir; S+L+(R): sofosbuvir + ledipasvir (with or without RBV) S+R+(P): sofosbuvir + RBV (with or without peg-IFN); S+V+(R): sofosbuvir + velpatasvir (with or without RBV); TE: treatment experienced; TN: treatment-naïve.

## INTRODUCTION

Hepatitis C virus (HCV) infection is a pressing global public health problem to be solved. There are 130-150 million people infected with chronic hepatitis C (CHC) globally, and about 350,000-500,000 patients die from HCV related liver diseases each year [1-3]. Hepatitis C virus has seven genotypes and each genotype (GT) consists of several subgroups, which display various distributing features around the world [4-6]. Furthermore, HCV GT is related to the antiviral effect. Approximately 75% HCV GT 2/3 infected patients, 40% HCV GT 1 infected patients and 43-70% HCV GT 4/5/6 infected patients will achieve sustained virological response (SVR) after treatment with peg-interferon (Peg-IFN) alfa combined with ribavirin (RBV) [7, 8]. Although the Peg-IFN alfa combined with RBV (P+R) treatment for patients with HCV GT 2/3 infections achieves a high SVR rate, the severe adverse effects (SAEs) and the low tolerability lead to suboptimal SVR rate [9, 10]. Consequently, the direct-acting antiviral agents (DAAs) represent a great progress in the antiviral therapy of HCV infection.

Sofosbuvir is an oral nucleotide analogue which can inhibit HCV-specific NS5B polymerase. Several randomized controlled trials (RCTs) have showed that sofosbuvir-

containing regimens for CHC have higher SVR rates, fewer side effects than P+R regimen, and reduce the duration of treatment by 2 to 4 times, particularly for HCV GT 2/3 infected patients [11-13]. In 2013, the US Food and Drug Administration (FDA) approved sofosbuvir combined with RBV for oral dual therapy of HCV GT 2/3 [14].

Currently, several reviews about sofosbuvir have been published. Some reviews only focused on the general scope of the problems, such as assessment of the pharmacology or partial clinical effects of sofosbuvir in the development process; others evaluated efficacy and safety for all genotypes. However, a comprehensive review on the efficacy and safety of sofosbuvir for HCV GT 2/3 infected CHC patients is not available. Therefore, we conducted a comprehensive analysis of the RCTs to explore the efficacy and safety of sofosbuvir in HCV GT 2/3 infected patients. This study can provide more detailed and effective drug information for medical professionals and researchers.

The aim of this study was to provide a comprehensive assessment of the efficacy and safety of sofosbuvir-containing regimens in patients with HCV GT 2/3 infection using data from 18 RCTs.

## METHODS

### Literature search

Two investigators independently performed a comprehensive electronic search on the PubMed, Web of Science databases, and the Cochrane Library from August 2016 to June 2017. PubMed search included sofosbuvir as keyword in the title / abstract field and limited term was randomized controlled trial. Sofosbuvir and randomized controlled trial were the search term used for The Cochrane Library database and the limits set were trial from all results. The literature searched on Web of Science databases was performed by using sofosbuvir and randomized controlled trial as the search topic. The strategy is shown in Fig 1.

### Inclusion and exclusion criteria

Only RCTs which met the following criteria were included: (1) evaluated HCV GT 2/3 infected patients; (2) sofosbuvir-containing regimens were administered; and (3) the primary endpoint was SVR12.

Studies were excluded if they: (1) did not include HCV GT 2/3 infected patients; (2) evaluated co-infected patients; (3) no sofosbuvir-containing regimens were administered; (4) the treatment duration was only 8 or 16 weeks; (5) did not provide the primary endpoint SVR12; (6) published in conference proceedings, reports and reviews, and (7) were not RCTs.

### Quality evaluation

All the trials included in the comprehensive analysis were assessed for methodological quality using the Cochrane Handbook for Systematic Reviews of Interventions 5.3 which contains the following content: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting, and other sources of bias. We divided each criterion into "yes", "no" or "unclear", and assessed the bias risk as "low bias risk", "high bias risk" and "unclear risk of bias."

### Endpoints measures

The efficacy of sofosbuvir-containing regimens was defined as the percentage of the SVR at week 12 after the end of treatment (SVR12) and at week 24 (SVR24), which were considered the endpoints. SVR12 was the primary endpoint.

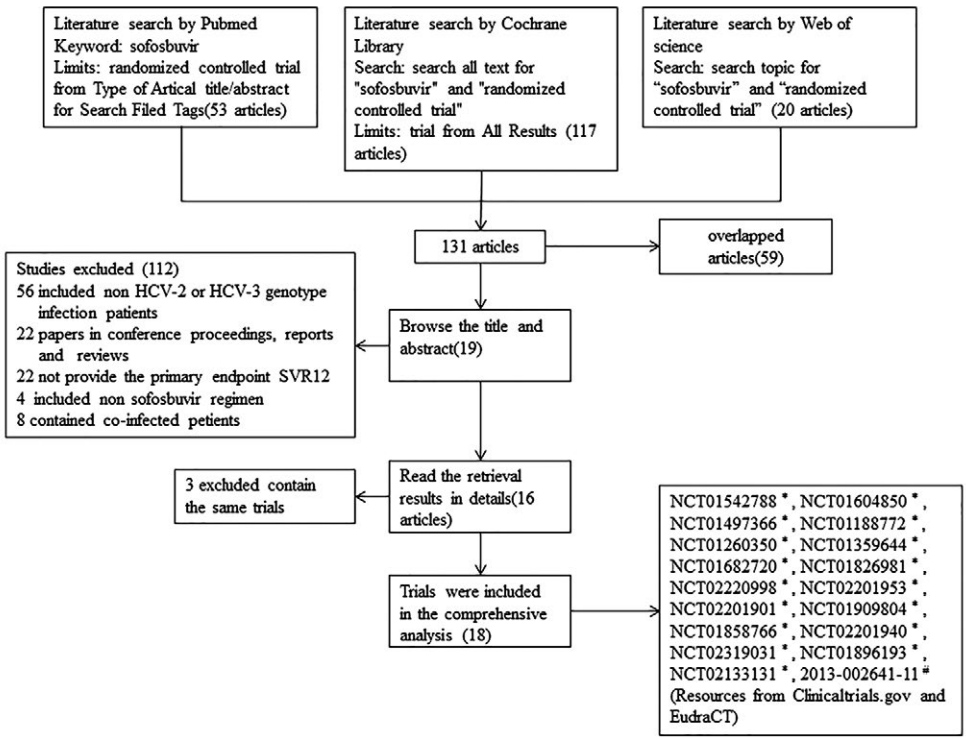


**Fig. 1.** Flowchart of the literature search and selection methods used. * Posted on the ClinicalTrials.gov website; # posted on the EudraCT website.

SVR12 or SVR24 were defined as a HCV RNA < the lower limit of quantitation (LLOQ) at follow-up of 12- or 24-weeks after cessation of therapy.

For the assessment of safety of sofosbuvir-containing regimen, the percentage of participants with the adverse events (AEs) and severe AEs (SAEs) was considered. The AEs were defined as any unfavorable medical event that was not related to the purpose of treatment in the course of normal use, dosage, and application of a drug for the prevention, diagnosis or treatment of the disease. The SAEs were defined as any event causing or prolonging hospitalization, resulting in disability, incapacity or death, or leading to congenital malformation or birth defects in the offspring of the clinical trial participants.

**Study selection and data extraction**

Two reviewers independently performed the study selection and data extraction: overlapped articles were excluded. Then, the two reviewers browsed the title and abstract of each article for identifying articles in accordance with the inclusion and exclusion criteria. The two reviewers read the retrieval results in detail and excluded articles containing the same trials.

The following data were collected: the first author's name, year of publication, study design, treatment regimen, number of patients, HCV GT, duration of treatment, history of treatments, presence of cirrhosis, age, sex, race, HCV RNA levels, IL28B genotype, alanine aminotransferase (ALT), and the endpoints measured as described above. The ClinicalTrials.gov website and EudraCT website were selected as the primary sources of data. Disagreement between the two reviewers was resolved by consensus if possible.

The treatment regimen in this study included sofosbuvir combined with daclatasvir (with or without RBV) or S+D+(R), sofosbuvir combined with RBV (with or without peg-IFN) or S+R+(P), sofosbuvir combined with velpatasvir (with or without RBV) or S+V+(R), and sofosbuvir combined with ledipasvir (with or without RBV) or S+L+(R), sofosbuvir combined with grazoprevir/elbasvir FDC (Fixed Dose Combination) or S+G+E (Table I).

**Statistical analyses**

Collected endpoints were dichotomous variables, and therefore, the effect sizes and 95% confidence intervals (CIs) were used to assess the efficacy and safety of sofosbuvir. To effectively evaluate the efficacy and safety of sofosbuvir, we conducted subgroup analyses of SVR12, SVR24, AEs, and SAEs by different duration of treatment, regimens, genotypes, history of treatments, and the presence or absence of cirrhosis. All statistical analyses were conducted using Stata13.0 software.

## RESULTS

The search term and limits described above were applied to search the PubMed, the Cochrane Library and Web of Science databases, and 53, 117 and 20 articles were identified respectively. First of all, 59 overlapped articles were excluded. After browsing the titles and abstracts, 112 studies were excluded based on the inclusion and exclusion criteria. Finally, 18 trials were included in this study after excluding 3 articles containing the same trials (Fig 1).

**Study and patients' characteristics**

Table I shows the basic characteristics of the 18 RCTs included in this study [15-30]. The methodological quality of each trial included in the comprehensive analysis are shown in Fig. 2. All the included trials had high methodological quality, especially with a lower selection bias.

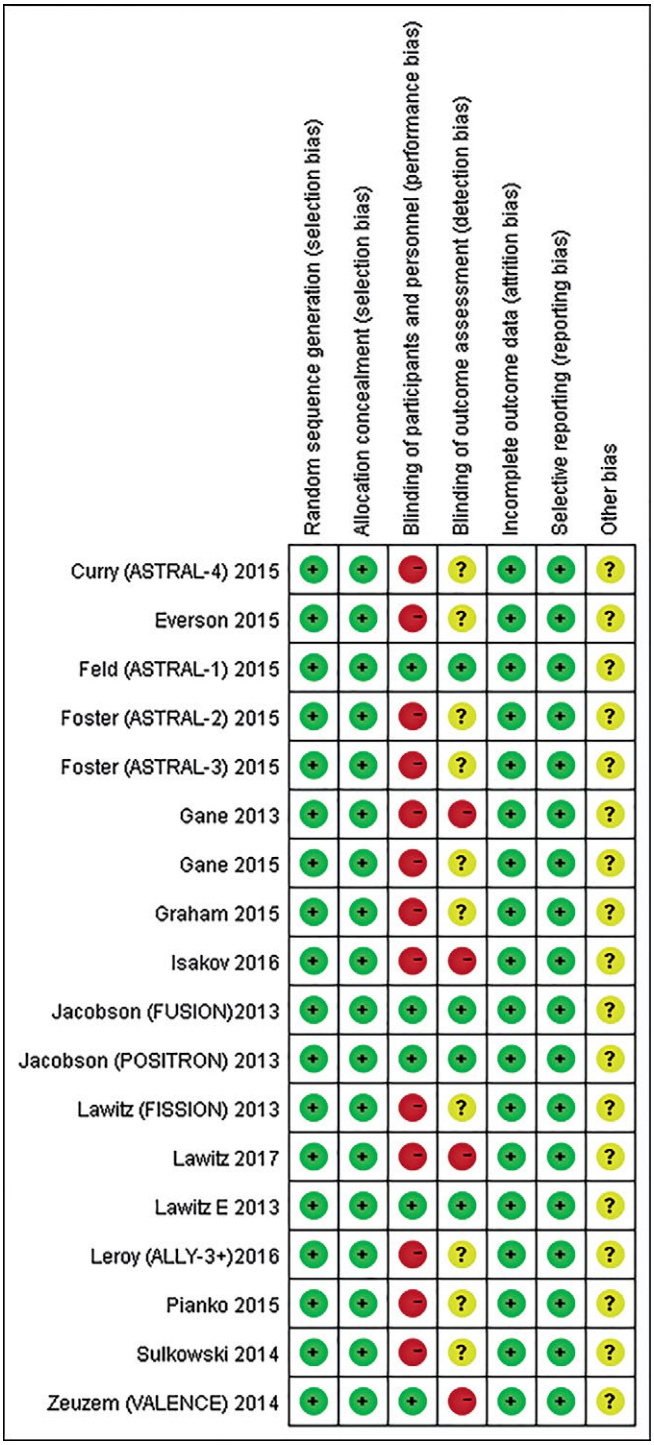


**Fig. 2**. Assessment of the quality of the studies included in the comprehensive analysis. + low bias risk; − high bias risk; ? unclear risk of bias.

The sofosbuvir-containing regimens group included 2,732 participants, while 243 participants were in the R+P regimen

**Table I**. Main characteristics of the studies and patients enrolled in this comprehensive analysis

| Author/year | Trials numbers | Treatment regimen | n | GT2/ GT3 | Duration (weeks) | Treatment history (TN/TE) | Cirrhosis (Yes/ No) | Age (year) | Male (%) | White race (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Jacobson (POSITRON) 2013 | NCT01542788* | S+R | 207 | 109/98 | 12 | 170/37 | 31/176 | 52 (50.6-53.4) | 117 (56.5) | 188 (90.8) |
| Jacobson (FUSION) 2013 | NCT01604850* | S+R | 103‡ | 36/64 | 12 | TE | 36/64 | 54 (52.5-55.5) | 73 (73.0) | 88 (87.0) |
| Lawitz (FISSION) 2013 | NCT01497366* | S+R | 256‡ | 70/183 | 12 | TN | 50/205 | 48 (46.7-49.3) | 171 (66.8) | 223 (88.1) |
| | | P+R** | 243‡ | 67/176 | 24 | TN | 50/189 | 48 (46.6-49.4) | 156 (64.2) | 212 (87.2) |
| Lawitz E 2013 | NCT01188772* | S+P+R | 25 | 15/10 | 12 | TN | No | 47 (42.6-51.8) | 16 (64.0) | 20 (80.0) |
| Gane 2015 | NCT01260350* | S+(P)+(R), S+L | 76 | 19/57 | 12 | 51/25 | No | 44 (39.8-48.2) | 50 (65.8) | 59 (77.6) |
| Sulkowski 2014 | NCT01359644* | S+D+(R) | 28 | 17/11† | 24 | TN | No | 49 (44.8-53.7) | 11(39.3) | 22 (57.9) |
| Zeuzem (VALENCE) 2014 | NCT01682720* | S+R | 334‡ | 73/261 | 12, 24 | 139/195 | 73/261 | 51 (38.2-64.2) | 201 (60.2) | 312 (93.4) |
| Gane 2015 | NCT01826981* | S+P+R, S+L+(R) | 111 | GT3 | 12 | 51/60 | 33/78 | 48 (38.9-57.9) | 71 (64.0) | 94 (84.7) |
| Graham 2015 | 2013-002641-11# | S+R+(P) | 396‡ | 33/363 | 12, 24 | 188/208 | 147/249 | 49 (35.6-63.3) | 261 (65.9) | 333 (84.1) |
| Foster (ASTRAL-2) 2015 | NCT02220998* | S+V, S+R | 266 | GT2 | 12 | 39/227 | 38/228 | 57 (38.5-75.5) | 158 (59.4) | 235 (88.3) |
| Foster (ASTRAL-3) 2015 | NCT02201953* | S+V | 552‡ | GT3 | 12, 24 | 410/142 | 163/389 | 49 (30.6-68.4) | 344 (62.3) | 489 (88.6) |
| Curry (ASTRAL-4) 2015 | NCT02201901* | S+V+(R) | 51 | 12/39† | 12, 24 | NA | Yes | NA | NA | NA |
| Pianko 2015 | NCT01909804* | S+V+(R) | 105 | GT3 | 12 | TE | 52/53 | 55 (53.8-56.2) | 75 (71.4) | 98 (93.3) |
| Everson 2015 | NCT01858766* | S+V | 37 | 10/27 | 12 | TN | No | 51 (46.8-55.2) | 24 (64.9) | 36 (97.3) |
| Feld (ASTRAL-1) 2015 | NCT02201940* | S+V | 104 | GT2 | 12 | 79/25 | 10/93 | NA | NA | 82 (78.8) |
| Leroy (ALLY-3+) 2016 | NCT02319031* | S+D+R | 24 | GT3 | 12 | 6/18 | Yes | 53 (49.7-56.3) | 18 (75.0) | 23 (95.8) |
| Isakov 2016 | NCT01896193* | S+R | 31 | GT3 | 24 | TN | 5/26 | 40 (36.5-43.5) | 19 (61.3) | 31 (100) |
| Lawitz 2017 | NCT02133131* | S+G+E | 26 | GT3 | 12 | TN | 12/14 | 48 (43.4-52.6) | 18 (69.2) | 26 (100) |

* Posted on the ClinicalTrials.gov website; # posted on the EudraCT website; ** control groups; † did not offer specific SVR12 rate; ‡ partial data lack
S: sofosbuvir; D: daclatasvir; R: ribavirin; L: ledipasvir; V: velpatasvir; P: pegylated interferon (Peg-IFN); G: grazoprevir; E: elbasvir; GT: genotype; TN: treatment-naive; TE: treatment-experienced; NA: not applicable.

group. In all patients of the sofosbuvir-containing regimens group, 764 patients were infected by HCV GT 2, and 1962 patients were infected by HCV GT 3, while for 6 patients GT was not available. There were 1,536 treatment-naïve (TN) patients and 1,145 and treatment experienced (TE) patients, for 51 patients the treatment history was not available. 725 patients had cirrhosis while 2002 patients did not have evidence of cirrhosis; in 5 patients data about cirrhosis status were not available. The mean age of patients in the included trials was 51±10.6 year. A percentage of 63.1% of patients enrolled were men and 88.0 % of patients enrolled were white race.

**Efficacy of Sofosbuvir**

***SVR12 and SVR24 rate***

A total of 18 trials were included for SVR12, the pooled estimate rate of SVR12 was 84.6% (95% CI: 83.2-86.0, Table II). A total of 14 trials were included for SVR24, the pooled estimate rate of SVR24 was 83.7% (95% CI: 82.0-85.2). We conducted subgroup analyses of SVR12 and SVR24 by different duration of treatment, regimens, genotypes, history of treatment, and the presence or absence of cirrhosis. As shown in Table II, the SVR12 and SVR24 rate did not have a statistically significant difference between the 12-weeks subgroup and 24-weeks subgroup. As for the different regimens, the S+V+(R) regimen presented higher beneficial effect on the SVR12 rate than the S+R+(P) regimen and S+L+(R) regimen (Table II), and the S+V+(R) and S+D+(R) regimen showed significantly higher SVR24 rate than the S+R+(P) regimen. Furthermore, all four sofosbuvir-containing regimens presented significantly superior SVR12 rate than the P+R regimen. The SVR12 rate of sofosbuvir-containing regimens for GT 2 infection was significantly higher than that for GT 3 infection (see Table II). As for the treatment history, the SVR12 rate of TN patients who received the sofosbuvir-containing regimens was significantly higher than the rate of TE patients. Cirrhotic patients presented significantly lower SVR12 rates than non-cirrhotic patients.

**Table II.** SVR12 and SVR24 rate

| Response | SVR12 (N=2726) | | SVR24 (N=2104) | |
|---|---|---|---|---|
| | Total, n/N | Rate (95%CI) % | Total, n/N | Rate (95%CI) % |
| Overall | 2307/2726 | 84.6 (83.2-86.0) | 1760/2104 | 83.7 (82.0-85.2) |
| By the different duration of treatment | | | | |
| 12 weeks | 1640/1927 | 85.1 (83.4-86.7) | 1272/1520 | 83.7 (81.7-85.5) |
| 24 weeks | 667/799 | 83.5 (80.7-86.0) | 488/584 | 83.6 (80.3-86.5) |
| By regimens | | | | |
| P+R | 162/243 | 66.7 (60.4-72.6) | 159/243 | 65.4 (59.1-71.4) |
| S+D+(R) | 46/52 | 89.7 (79.9-95.8) | 48/52 | 92.3 (81.5-97.9) |
| S+L+(R) | 91/111 | 82.0 (73.6-88.6) | 83/101 | 81.2 (73.3-89.1) |
| S+R+(P) | 1468/1819 | 80.7 (78.8-82.5) | 1089/1388 | 78.5 (76.2-80.6) |
| S+V+(R) | 672/708 | 94.9 (93.0-96.4) | 534/553 | 96.6 (94.7-97.9) |
| S+G+E | 24/26 | 92.3 (74.9-99.1) | -- | -- |
| By genotypes | | | | |
| GT2 | 690/721 | 95.7 (94.0-97.1) | 88/94 | 96.2 (93.6-97.1) |
| GT3 | 1532/1897 | 80.8 (78.9-82.5) | 987/1130 | 87.3 (85.3-89.2) |
| By treatment history | | | | |
| TN patients | 1290/1492 | 86.5 (84.6-88.2) | 351/456 | 77.0 (72.8-80.8) |
| TE patients | 721/906 | 79.6 (76.8-82.2) | 202/265 | 76.2 (70.6-81.2) |
| By the presence or absence of cirrhosis | | | | |
| Cirrhosis | 485/651 | 74.5 (71.0-77.8) | 55/58 | 94.8 (85.6-98.9) |
| Non-cirrhosis | 1492/1708 | 87.4 (85.7-88.9) | 185/194 | 95.4 (91.4-97.9) |

P+R peg-IFN combine RBV; S+D+(R) sofosbuvir combine daclatasvir (with or without RBV); S+L+(R) sofosbuvir combine ledipasvir (with or without RBV); S+R+(P) sofosbuvir combine RBV (with or without peg-IFN); S+V+(R) sofosbuvir combine velpatasvir (with or without RBV); S+G+E sofosbuvir combine grazoprevir/elbasvir FDC (Fixed Dose Combination); GT genotype; TN treatment-naive; TE treatment-experienced.

***SVR12 rate by subgroup***

We conducted subgroup analyses of SVR12 in HCV GT 2 and GT 3 infected patients by a different duration of treatment, regimens, treatment history, the presence and absence of cirrhosis, sex, age, race, IL 28B genotype, baseline HCV RNA, and baseline ALT. As shown in the table III, in HCV GT 2 and GT 3 infected patients, the SVR12 rates for the S+V+(R) regimen were 99.2% (95% CI: 97.2-99.9) and 92.4% (95% CI: 89.6-94.7), which were higher than that for S+R+(P) regimen. In HCV GT 3 infected patients, the TN subgroup presented higher beneficial effect on the SVR12 rate than the TE subgroup. The cirrhosis subgroup showed lower SVR12 rate than the non-cirrhosis subgroup. And the male subgroup also showed a lower SVR12 rate than the female subgroup (Table III)

**Safety of Sofosbuvir**

***AEs and SAEs rate***

Twelve trials reported the incidence of AEs; the pooled estimate AEs rate was 83.8% (95% CI: 82.3-85.3, Table IV). Thirteen trials were included for SAEs; the pooled estimate SAEs rate was 3.9% (95% CI: 3.2-4.8). An analysis for the rate of AEs leading to discontinuation and the common AEs were conducted. The results showed that the overall rate of discontinuation due to AEs was 1.2% (95% CI: 0.8-1.7). Furthermore, the common AEs were fatigue (33.7%), headache (29.3%), nausea (18.9%), insomnia (18.3%), pruritus (10.9%), and irritability (10.0%).

***AEs and SAEs rate by subgroup***

Based on different durations of treatment, regimens, genotypes, history of treatment, and the presence or absence of cirrhosis, we conducted subgroup analyses. The results are shown in Table V. The subgroup of patients treated for 12-weeks showed significantly lower AEs rate than the subgroup treated for 24-weeks. The rate of SAEs did not show a statistically significant difference among the different durations of treatments. As for the different regimens, we found that AEs rate of the S+V+(R) regimen subgroup was significantly lower than the S+R+(P) regimen and S+L+(R) regimen. The SAEs rate of the S+V+(R) regimen subgroup was significantly lower than the S+D+(R) regimen subgroup. Furthermore, the rate of AEs of P+R regimen was 97.1% (95% CI: 94.2-98.8), which was significantly higher than all four sofosbuvir-containing regimens. For different GTs, the GT 2 subgroup showed lower AEs rate than the GT 3 subgroup.

## DISCUSSION

For the last few years, an important advancement has been achieved in the treatment of CHC with DAAs, which directly inhibit the replication cycle of HCV. Sofosbuvir, one of the DAAs, has been proven to be effective for HCV GT

**Table III.** Subgroup analysis of SVR12

| Response | GT2 (N=721) | | GT3 (N=1897) | |
|---|---|---|---|---|
| | Total, n/N | Rate % (95%CI) | Total, n/N | Rate (95%CI) % |
| Overall | 690/721 | 95.7 (94-0,97.1) | 1532/1897 | 80.8 (78.9-82.5) |
| By the different duration of treatment | | | | |
| 12 weeks | 670/700 | 95.7 (93.9-97.1) | 910/1147 | 79.3 (76.9-81.6) |
| 24 weeks | 20/21 | 95.2 (76.2-99.9) | 622/750 | 82.9 (80.0-85.6) |
| By regimens | | | | |
| PR | 52/67 | 77.6 (65.8-86.9) | 110/176 | 62.5 (54.5-69.7) |
| S+D+(R) | -- | -- | 21/24 | 87.5 (67.6-97.3) |
| S+L+(R) | -- | -- | 83/101 | 82.2 (73.3-89.1) |
| S+R+(P) | 432/461 | 93.7 (91.1-95.7) | 990/1298 | 76.3 (73.9-78.6) |
| S+V+(R) | 258/260 | 99.2 (97.2-99.9) | 414/448 | 92.4 (89.6-94.7) |
| S+G+E | -- | -- | 24/26 | 92.3 (74.9-99.1) |
| By treatment history | | | | |
| TN patients | 196/199 | 98.5 (95.7-99.7) | 886/1040 | 85.2 (82.9-87.3) |
| TE patients | 125/135 | 92.6 (86.8-96.4) | 558/709 | 78.7 (75.5-81.7) |
| By the presence or absence of cirrhosis | | | | |
| Cirrhosis | 84/93 | 90.3 (82.4-95.5) | 395/535 | 73.8 (69.9-77.5) |
| Non-cirrhosis | 280/291 | 96.2 (93.3-98.1) | 1019/1153 | 88.4 (86.4-90.2) |
| By sex | | | | |
| Male | 122/126 | 96.8 (92.1-99.1) | 714/839 | 85.1 (82.5-87.4) |
| Female | 92/94 | 97.9 (92.5,99.7) | 457/486 | 94.0 (91.5-96.0) |
| By age | | | | |
| ≥65 years | 34/34 | 100.0 (89.7-100.0)* | 135/168 | 80.4 (73.5-86.1) |
| <65 years | 102/103 | 99.0 (94.7-100.0) | 933/1052 | 88.7 (86.6-90.5) |
| By race | | | | |
| Black | 14/14 | 100.0 (76.8-100.0)* | 8/8 | 100.0 (63.1-100.0)* |
| Non-black | 121/122 | 99.2 (95.5-100.0) | 996/1116 | 89.2 (87.3-91.0) |
| By IL 28B genotype | | | | |
| CC | 72/73 | 98.6 (92.6-100.0) | 450/505 | 89.1 (86.1-91.7) |
| Non-CC | 142/147 | 96.6 (92.2-98.9) | 719/820 | 87.7 (85.2-89.9) |
| By baseline HCV RNA | | | | |
| < 6 log10 IU/mL | 17/20 | 85.0 (62.1-96.8) | 196/213 | 92.0 (87.5-95.3) |
| ≥6 log10 IU/mL | 83/86 | 96.5 (90.1-99.3) | 359/424 | 84.7 (80.9-88.0) |
| By baseline ALT | | | | |
| ≤1.5×ULN | 48/52 | 92.3 (81.5-97.9) | 359/391 | 91.8 (88.6-94.3) |
| > 1.5×ULN | 52/54 | 96.3 (87.3-99.5) | 741/858 | 86.3 (83.9-88.6) |

* one-sided, 97.5% confidence interval. P+R peg-IFN combined with RBV; S+D+(R) sofosbuvir combined with daclatasvir (with or without RBV); S+L+(R)sofosbuvir combine with ledipasvir (with or without RBV); S+R+(P)sofosbuvir combined with RBV (with or without peg-IFN); S+V+(R)sofosbuvir combined with velpatasvir (with or without RBV); S+G+E sofosbuvir combined with grazoprevir/elbasvir FDC (Fixed Dose Combination); GT genotype; TN treatment-naïve; TE treatment-experienced.

1-6 infection. In addition, studies have found that GT 2/3 infected patients often show a better antiviral response than GT 1/4 infected patients [31]. The current comprehensive analysis, which included 18 trials evaluating 2,975 HCV GT 2/3 infected patients, attempted to explore the overall efficacy and safety of the sofosbuvir-containing regimens for HCV GT 2/3 infection. We assessed the overall efficacy with the SVR12 and SVR24 rate. For all the HCV GT 2/3 infected patients, the pooled SVR12 rate was 84.6% (95% CI: 83.2-86.0), and the pooled SVR24 rate was 83.7% (95% CI: 82.0-85.2). The SVR12 and SVR24 rate were concordant in clinical trials with Peg-IFN and DAA-containing regimens [32]. Adverse events and SAEs rate were used to assess the overall safety. The pooled rates of AEs was 83.8% (95% CI: 82.3-85.3), and the pooled SAEs rate was 3.9% (95% CI: 3.2-4.8). Furthermore, the overall AEs rate leading to discontinuation was only 1.2% (95% CI: 0.8-1.7). However, the FISSION study discovered that the rate of discontinuation was 11% in HCV GT 2/3

**Table IV.** Rate of AEs, SAEs, discontinuation and the common AEs

| Response | Total, n/N | Rate % (95%CI) |
|---|---|---|
| Total AEs (not including SAEs) | 1992/2376 | 83.8 (82.3-85.3) |
| SAEs | 94/2404 | 3.9 (3.2-4.8) |
| AEs leading to discontinuation | 28/2382 | 1.2 (0.8-1.7) |
| Fatigue | 800/2376 | 33.7 (31.8-35.6) |
| Headache | 695/2376 | 29.3 (27.4-31.1) |
| Nausea | 448/2376 | 18.9 (17.3-20.5) |
| Insomnia | 429/2350 | 18.3 (16.7-19.9) |
| Pruritus | 259/2376 | 10.9 (9.7-12.2) |
| Irritability | 234/2350 | 10.0 (8.8-11.2) |

AE: adverse event; SAE: severe adverse event; n: number of occurrences of each outcome; N: total number of trials containing the corresponding outcomes.

infected patients receiving 24-weeks of the P+R regimen [27]. The current comprehensive analysis found that HCV GT 2/3 infected patients who received sofosbuvir-containing regimens appeared to have the common AEs, such as fatigue, headache, nausea, insomnia, pruritus, and Irritability.

Subgroup analyses revealed that the subgroup of the S+V+(R) regimen showed significantly higher efficacy than the subgroup of the S+R+(P) regimen and S+L+(R) regimen (94.9% vs. 80.7% and 82.0% for SVR12 rate; 96.6% vs. 78.5% and 81.2% for SVR24 rate). This subgroup also showed significantly higher safety than the subgroup of the S+R+(P) regimen and S+L+(R) regimen (69.3% vs. 87.7% and 87.4% for AEs rate). Furthermore, all four sofosbuvir-containing regimens presented significantly higher SVR12 rate and lower AEs than the PR regimen. Likewise, previous research showed that compared to traditional regimen, sofosbuvir-containing regimens provide a higher cure rate [33]. The current analysis confirmed that the sofosbuvir-containing regimens showed better efficacy and safety for HCV GT 2/3 infected patients than the traditional regimen, and revealed that the S+V+(R) regimen represents the best option in the currently recommended sofosbuvir-containing regimens. As for the treatment duration, in HCV GT 2 and GT 3 infected patients, 12 weeks and 24 weeks were recommended by the joint American Association for the Study of Liver Diseases (AASLD) / the Infectious Diseases Society of America (IDSA), respectively [33]. Therefore, only 38 (5.0%) of the 764 HCV GT 2 infected patients received 24 weeks of treatment with sofosbuvir-containing regimens; 761 (38.8%) of the 1,962 HCV GT 3 infected patients received 24 weeks of treatment with sofosbuvir-containing regimens. Previous research has shown that for patients with HCV GT 3 infection, treatment with S + R regimens for 24 weeks was more effective than treatment for 12 and 16 weeks [34]. However, the optimum treatment duration of other sofosbuvir-containing regimens requires more studies.

Cirrhosis caused by HCV can lead to severe outcomes, such as hepatocellular carcinoma or liver transplantation [34]. The cirrhotic patients achieve lower SVR rates than those without

**Table V**. Subgroup analysis of adverse events (AE) and severe adverse events (SAE)

| Response | AEs (N=2249) | | SAEs (N=2293) | |
|---|---|---|---|---|
| | Total, n/N | Rate (95%CI) % | Total, n/N | Rate (95%CI) % |
| Overall | 1992/2376 | 83.8 (82.3-85.3) | 94/2404 | 3.9 (3.2-4.8) |
| By the different duration of treatment | | | | |
| 12 weeks | 1342/1652 | 81.2 (79.3-83.1) | 54/1652 | 3.3 (2.5-4.2) |
| 24 weeks | 650/724 | 89.8 (87.3-91.9) | 40/752 | 5.3 (3.8-7.2) |
| By regimens | | | | |
| PR | 236/243 | 97.1 (94.2-98.8) | 3/243 | 1.2 (0.2-3.6) |
| S+D+(R) | 21/24 | 87.5 (67.6-97.3) | 7/52 | 13.5 (5.6-25.8) |
| S+L+(R) | 97/111 | 87.4 (79.7-92.9) | 5/111 | 4.5 (1.5-10.2) |
| S+R+(P) | 1573/1794 | 87.7 (86.1-89.2) | 73/1794 | 4.1 (3.2-5.1) |
| S+V+(R) | 285/411 | 69.3 (64.6-73.8) | 8/414 | 1.9 (0.8-3.8) |
| S+G+E | 6/26 | 23.1 (9.0-43.6) | 1/26 | 3.8 (0.1-19.6) |
| By genotypes | | | | |
| GT2 | 164/277 | 59.2 (53.2-65.0) | 4/573 | 0.7 (0.2-1.8) |
| GT3 | 845/993 | 85.1 (82.7-87.3) | 39/1024 | 3.8 (2.7-5.2) |
| By treatment history | | | | |
| TN patients | 344/409 | 84.1 (80.2-87.5) | 18/471 | 3.8 (2.3-6.0) |
| TE patients | 169/188 | 89.9 (84.7-93.8) | 6/238 | 2.5 (0.9-5.4) |
| By the presence or absence of cirrhosis | | | | |
| Cirrhosis | 4/13 | 30.8 (9.1-60.4) | 1/32 | 3.1 (0.1,1-6.2) |
| Non-cirrhosis | 108/124 | 87.1 (78.9-92.4) | 6/244 | 2.5 (0.9-5.3) |

P+R peg-IFN combined with RBV; S+D+(R) sofosbuvir combined with daclatasvir (with or without RBV); S+L+(R)sofosbuvir combined with ledipasvir (with or without RBV); S+R+(P)sofosbuvir combined with RBV (with or without peg-IFN) ; S+V+(R)sofosbuvir combined with velpatasvir (with or without RBV); S+G+E sofosbuvir combined with grazoprevir/elbasvir FDC (Fixed Dose Combination); GT genotype; TN treatment-naïve; TE treatment-experienced

cirrhosis. The cirrhotic patients with HCV GT 3 treated with the S + D regimen for 12 weeks had a lower SVR24 rate than patients without cirrhosis [35]. Genotype 3 infected cirrhotic patients who were TE, treated with the S+L+R regimen for 12-weeks showed a lower SVR12 rate than patients without cirrhosis [17]. Similarly, our subgroup analysis of cirrhosis confirmed that the sofosbuvir-containing regimens for cirrhotic patients resulting from HCV GT 2/3 infections presented a lower efficacy than non-cirrhotic patients (74.5% vs. 87.4% for SVR12 rate), especially in HCV GT 3 infected patients (73.8% vs. 88.4% for SVR12). As for the treatment history, subgroup analyses showed that the subgroup of TN patients had a better efficacy than the subgroup of TE patients (86.5% vs. 79.6% for SVR12 rate).

The previous studies showed that a different HCV GTs infection influenced the progression of chronic hepatitis. For example, GT 2 infected patients are more likely to get a higher ALT level, while GT 3 infected patients showed faster progression of chronic hepatitis and higher mortality [36, 37]. The current analysis confirmed that the sofosbuvir-containing regimens in patients with HCV GT 2 infection had significantly better efficacy and safety than in patients infected with GT 3 (95.7% vs. 80.8% for SVR12 rate; 59.2% vs. 85.1% for AEs rate; 0.7% vs. 3.8% for SAEs rate).

In HCV GT 2 infected patients, the efficacy of the S+V+(R) regimen was consistently higher than the S+R+(P) regimen (99.2% vs. 93.7%). According to recommendations of the AASLD and European Association for the Study of the Liver (EASL) in 2015 [33], for patients with HCV GT 2 infection the preferred regimen is S+R. The current study found that S+V+(R) regimen may be a more effective regimen. However, no significant differences were found in other subgroup analysis. Nevertheless, there was no sufficient evidence to prove the different curative effect among these subgroups, due to the few GT 2 infected patients included in this analysis, especially the subgroup of 24-weeks, cirrhosis, male and female. Therefore, more patients should be included in clinical trials to obtain sufficient evidence.

In HCV GT 3 infected patients, the sofosbuvir-containing regimens for patients who were TN, non-cirrhosis, female, or less than 60 years old were significantly better than for patients who were TE, cirrhosis, male, or more than 60 years old (85.2% vs. 78.7%; 88.4% vs.73.8%; 94.0% vs. 85.1%; 88.7% vs. 80.4%, all for SVR12 rate). Therefore, we reason that patients who were TE, cirrhotics, male, or more than 60 years old are the hard-to-cure, whom we should put a top priority when the sofosbuvir-containing regimens were presented to patients with HCV GT 3 infection. According to the recommendations of AASLD and EASL in 2015 [33], in patients with HCV GT 3 infection the preferred regimen is S+D+(R). The current study found that in patients with HCV GT 3 the SVR12 rates were consistenly higher in S+V+(R) regimen subgroup than in S+D+(R) (92.4% vs. 87.5%) but without statistically significant difference. However, only one study evaluated the efficacy of the S+D+(R) regimen for treating GT 3 patients and included only 24 patients, so more studies are required.

The sofosbuvir-containing regimens in patients with HCV GT 2/3 infections have better efficacy and safety than the P+R regimen. However, sofosbuvir is more expensive than boceprevir or telaprevir combined P+R regimens [38, 39]. Therefore, for patients who are struggling to pay for the treatment, the sofosbuvir-containing regimens are only recommended for HCV GT 2 infected patients or non-cirrhotic patients caused by HCV GT 2/3 infections. The S+V+(R) regimens are the better option for treatment than other sofosbuvir-containing regimens.

There are several strengths in our comprehensive analysis. First, this study was the first study to explore the efficacy and safety of sofosbuvir for HCV GT 2/3 infections. Besides, the 18 RCTs included in the comprehensive analysis were all of high quality. In addition, we provided the pooled SVR12, SVR24, AE, SAE rates in the various subgroups and their 95% CI, which may provide a reference for further studies, and help the clinicians select the best sofosbuvir-containing regimens for patients with HCV GT 2/3 infection.

This study also had some limitations. Firstly, due to the limitations of the extracted data, we only analyzed the appropriate efficacy and safety rate and its 95% CI and failed to analyze the relative risk (RR) for the various subgroups. Secondly, only one trial of this study included the traditional therapy, the P+R regimen. In addition, some studies included two treatment doses of velpatasvir for 8 weeks or 16 weeks, but we failed to conduct subgroup analysis on the drug doses because there were few relevant studies.

## CONCLUSIONS

Our comprehensive analysis supports that the sofosbuvir-containing regimens for patients with HCV GT 2/3 infection have better efficacy and safety than the P+R regimen. The S+V+(R) regimen proved to be the best regimen in the currently recommended sofosbuvir-containing regimens. Furthermore, the sofosbuvir-containing regimens in patients with HCV GT 2 infection have better efficacy than in patients with HCV GT 3 infection.

**Conflicts of interest**: The authors declare no conflict of interest.

**Authors' contributions:** HF, PH, and YZ participated in the design of the study. HF, TT, JW, XX, and XF took charge of literature retrieval, data collection and quality control. HF, PH, and TT performed the statistical analysis. JW, RY, and MY contributed to analysis. HF, PH, and TT wrote the paper. All authors read and approved the final manuscript.

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## REFERENCES

1. Maruyama A, Partovi N, Yoshida EM, Erb SR, Azalgara VM, Hussaini T. A review of direct-acting antivirals for the treatment of hepatitis C in

patients with advanced chronic kidney disease. Nephrol Dial Transplant 2017;32:35-41. doi:10.1093/ndt/gfv361

2 Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-2128. doi:10.1016/S0140-6736(12)61728-0

3. Latt NL, Araz F, Alachkar N, Durand CM, Gurakar A. Management of hepatitis C infection among patients with renal failure. Minerva Gastroenterol Dietol 2015;61:39-49.

4. Cornberg M, Razavi HA, Alberti A, et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int 2011;31 Suppl 2:30-60. doi:10.1111/j.1478-3231.2011.02539.x

5. Zein NN. Clinical significance of hepatitis C virus genotypes. Clin Microbiol Rev 2000;13:223-235. doi:10.1128/CMR.13.2.223-235.2000

6. Candotti D, Temple J, Sarkodie F, Allain JP. Frequent recovery and broad genotype 2 diversity characterize hepatitis C virus infection in Ghana, West Africa. J Virol 2003;77:7914-923. doi:10.1128/JVI.77.14.7914-7923.2003

7. Chayama K, Hayes CN. Hepatitis C virus: How genetic variability affects pathobiology of disease. J Gastroenterol Hepatol 2011;**26 Suppl 1**:83-95. doi:10.1111/j.1440-1746.2010.06550.x

8. Antaki N, Craxi A, Kamal S, et al. The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report. Liver Int 2010;30:342-355. doi:10.1111/j.1478-3231.2009.02188.x

9. Sulkowski MS, Cooper C, Hunyady B, et al. Management of adverse effects of Peg-IFN and ribavirin therapy for hepatitis C. Nat Rev Gastroenterol Hepatol 2011;8:212-223. doi:10.1038/nrgastro.2011.21

10. Calvaruso V, Mazza M, Almasio PL. Pegylated-interferon-alpha(2a) in clinical practice: how to manage patients suffering from side effects. Expert Opin Drug Saf 2011;10:429-435. doi:10.1517/14740338.2011.559161

11. Tran TT. A review of standard and newer treatment strategies in hepatitis C. Am J Manag Care 2012;18:S340-S349.

12. Berden FA, Kievit W, Baak LC, et al. Dutch guidance for the treatment of chronic hepatitis C virus infection in a new therapeutic era. Neth J Med 2014;72:388-400.

13. Cholongitas E, Papatheodoridis GV. Sofosbuvir: a novel oral agent for chronic hepatitis C. Ann Gastroenterol 2014;27:331-337.

14. Tucker ME. FDA approve game changer hepatitis C drug sofosbuvir. Medscape Medical News. December 06, 2013. Available at: https://www.medscape.com/viewarticle/817371

15. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014;370:211-221. doi:10.1056/NEJMoa1306218

16. Leroy V, Angus P, Bronowicki JP, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). Hepatology 2016;63:1430-1441. doi:10.1002/hep.28473

17. Gane EJ, Hyland RH, An D, et al. Efficacy of Ledipasvir and Sofosbuvir, With or Without Ribavirin, for 12 Weeks in Patients With HCV Genotype 3 or 6 Infection. Gastroenterology 2015;149:1454-1461. doi:10.1053/j.gastro.2015.07.063

18. Isakov V, Zhdanov K, Kersey K, et al. Efficacy of sofosbuvir plus ribavirin in treatment-naive patients with genotype-1 and -3 HCV infection: results from a Russian Phase IIIb study. Antivir Ther 2016;21:671-678. doi:10.3851/IMP3065

19 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. doi:10.1053/j.gastro.2015.07.043

20. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med 2013;368:34-44. doi:10.1056/NEJMoa1208953

21. Lawitz E, Poordad F, Gutierrez JA, et al. Short-duration treatment with elbasvir/grazoprevir and sofosbuvir for hepatitis C: A randomized trial. Hepatology 2017;65:439-450. doi:10.1002/hep.28877

22. 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. doi:10.1056/NEJMoa1316145

23. Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med 2015;373:2599-2607. doi:10.1056/NEJMoa1512610

24. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med 2015;373:2608-2617. doi:10.1056/NEJMoa1512612

25. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. N Engl J Med 2015;373:2618-2628. doi:10.1056/NEJMoa1512614

26. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. New Engl J Med 2013;368:1867-1877. doi:10.1056/NEJMoa1214854

27. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878-1887. doi:10.1056/NEJMoa1214853

28. Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. Lancet Infect Dis 2013;13:401-408. doi:10.1016/S1473-3099(13)70033-1

29. Pianko S, Flamm SL, Shiffman ML, et al. Sofosbuvir Plus Velpatasvir Combination Therapy for Treatment-Experienced Patients With Genotype 1 or 3 Hepatitis C Virus Infection: A Randomized Trial. Ann Intern Med 2015;163:809. doi:10.7326/M15-1014

30. Everson GT, Towner WJ, Davis MN, et al. Sofosbuvir With Velpatasvir in Treatment-Naive Noncirrhotic Patients With Genotype 1 to 6 Hepatitis C Virus Infection: A Randomized Trial. Ann Intern Med 2015;163:818-826. doi:10.7326/M15-1000

31. Zhu Y, Chen S. Antiviral treatment of hepatitis C virus infection and factors affecting efficacy. World J Gastroenterol 2013;19:8963-8973. doi:10.3748/wjg.v19.i47.8963

32. Thorlund K, Druyts E, Mills EJ. SVR12 is higher than SVR24 in treatment-naive hepatitis C genotype 1 patients treated with peginterferon plus ribavirin. Clin Epidemiol 2014;6:49-58. doi:10.2147/CLEP.S53302

33. 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. doi:10.1002/hep.27950

34. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson Jl, Loscalzo J. (Eds.). Harrison's Principles of Internal Medicine. 18th edn. Available at: http://accessmedicine.mhmedical.com/book.aspx?bookid=1140.

35. Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology 2015;61:1127-1135. doi:10.1002/hep.27726

36. Hiraga N, Suzuki F, Akuta N, et al. Clinical and virological characteristics of untreated patients with chronic hepatitis C who develop serum

alanine aminotransferase flare-up. J Med Virol 2005;75:240-248. doi:10.1002/jmv.20263

37. Bochud PY, Cai T, Overbeck K, et al. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. J Hepatol 2009;51:655-666. doi:10.1016/j.jhep.2009.05.016
38. Boseley S. Hepatitis C drug delayed by NHS due to high cost. The Guardian 16 Jan 2015. Available at: https://www.theguardian.com/society/2015/jan/16/sofosbuvir-hepatitis-c-drug-nhs
39. Yang HJ, Ryoo JY, Yoo BK. Meta-analysis of the efficacy and safety of sofosbuvir for the treatment of hepatitis C virus infection. Int J Clin Pharm 2015;37:698-708. doi:10.1007/s11096-015-0144-x