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Original article

Efficacy of 12-weeks velpatasvir plus sofosbuvir-based regimen in HCV-naive subjects with mild fibrosis: a meta-analysis

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Summary. *Background and aims:* In literature systematic data on treatment with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks in anti-HCV/HCV RNA positive subjects with mild fibrosis and naïve to previous Interferon free regimen are scanty. A meta-analysis has been performed to evaluate the efficacy of velpatasvir plus sofosbuvir combination in these patients. *Methods:* All randomized or non-randomized studies, investigating the sustained virological response rate to sofosbuvir plus velpatasvir without ribavirin for 12 weeks in subjects naïve to previous DAA therapy and with fibrosis F0-F2 or F0-F3, were included in the meta-analysis. *Results:* A total of 16 studies enrolling 4,907 subjects met the inclusion criteria and were included in this meta-analysis. The prevalence of SVR by sofosbuvir and velpatasvir was 98% (95% CI 96-99%) in the 4,907 subjects without cirrhosis. The prevalence of SVR was similar considering the 9 clinical studies and the 7 real-world studies (98%, CI 95%: 96-99% and 98%; CI 95%: 96-99%, respectively). Considering the 4 studies enrolling 1,371 subjects without advanced liver fibrosis the prevalence of SVR was also high [96% (95% CI: 94-98%)]. Data indicate a prevalence of SVR ranging to 95-100% according to the different HCV genotypes. *Conclusion:* Sofosbuvir plus velpatasvir therapeutic regimen was highly effective in HCV patients without advanced liver disease naïve to previous DAA regimen independently the different HCV genotypes. (www.actabiomedica.it)

Key words: velpatasvir, sofosbuvir, hepatitis C, mild fibrosis, HCV infection, initial fibrosis

Introducion

The World Health Organization has estimated that 71 million people are infected with hepatitis C virus (HCV) worldwide and that more than 399,000 people die each year of HCV-related liver diseases (1).

Since 2014 regimens without interferon, which combine several classes of directly acting antiviral agents (DAAs), have improved the response rate and tolerability. Nowadays, thanks to the high and rapid effect of the DAAs regimen, Interferon-free regimens yield a sustained virological response rate at week 12 (SVR12) of approximately 95%, even in patients with advanced liver diseases (2, 3).

Among DAAs, the NS5B nucleotide inhibitor (sofosbuvir) is effective agains all HCV genotypes with a favorable safety profile and a low risk for development of resistance; velpatasvir is an inhibitor of the HCV NS5A protein with a potent activity against all HCV genotypes. Several randomized controlled trails (RCTs) have evaluated the efficacy of this combination (sofosbuvir plus velpatasvir) with or without ribavirin in the treatment of different HCV genotypes showing a high efficacy. Thus, treatment-naïve and treatment-

experienced patients infected with different HCV genotypes, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, could be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (2, 3).

Few data are available in literature on the efficacy of this combination in subjects without advanced liver disease, when ribavirin is not indicated, especially in real-word scenario. Thus, a meta-analysis has been conducted to evaluate the efficacy of velpatasvir plus sofosbuvir combination without ribavirin for 12 weeks, assessed as sustained virological response at week 12 after the stop of therapy, in anti-HCV/HCV RNA positive subjects without advanced fibrosis and naïve to Interferon-free regimen.

Methods

Search strategy and selection criteria

The present systematic review and meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE).

Two researchers (LO and AR) conducted a comprehensive computerized literature search to identify original reports using MEDLINE and the Cochrane Library from January 2015 to March 2019, involving both medical subject heading (MeSH) terminology and relevant keywords for search strings to locate articles that analyzed the efficacy of velpatasvir plus sofosbuvir combination in anti-HCV/HCV RNA positive subjects without cirrhosis and advanced fibrosis and naïve to Interferon-free regimen.

The following items were used to search the studies: "Velpatasvir", "HCV infection", "HCV hepatitis". In addition, the reference lists of all studies meeting the inclusion criteria, of the studies excluded and of the published review articles were manually searched to identify any other study that might merit inclusion.

All studies included had to fulfill the following characteristics and inclusion criteria: (a) they presented original data from randomized or non-randomized trials; (b) they investigated the efficacy of sofosbuvir plus velpatasvir without ribavirin for 12 weeks in subjects without cirrhosis or advanced fibrosis, naïve to previous DAA therapy; (c) identified fibrosis by liver histology according to Metavir score (F0-F3 score for patients without cirrhosis and F0-F2 for those without advanced fibrosis) or Fibroscan (Transient Elastography-TE <12.5Pa for patients without cirrhosis and TE <9.5 for those without advanced fibrosis) or FIB-4 (score<3.25 for patients without cirrhosis and <1.45 for those without advanced fibrosis) or APRI (score <1 for patients without cirrhosis and <0.70 for those without advanced fibrosis) or Fibro-test (score <0.75 for patients without cirrhosis and <0.58 for those without advanced fibrosis); (d) report the primary outcomes clearly defined as Sustained Virological Response 12 (SVR), undetectable HCV RNA 12 weeks after therapy completion; (e) were available as a full text manuscript; (f) were written in the English language, and (g) were published online and indexed up to March 2019. The exclusion criteria of the meta-analysis were: (a) meta-analyses, letters, reviews, meeting abstracts, or editorial comments; (b) studies using ribavirin; (c) investigating patients with advanced liver fibrosis or cirrhosis did not reporting separate data for mild fibrosis. If more than one publication dealt with the same patient population and offered the same outcome messages, only the most recent or most complete article was included in the analysis.

Data extraction

Two reviewers (LO and AR) working independently extracted the data using a standard protocol and data-collection form according to the inclusion criteria. The following relevant information was collected from every article selected according to the inclusion criteria: last name of the first author, year of publication, country where the population was investigated, study design, sample size, participant characteristics (age range, sex), HCV genotype, type of methods used to stage liver disease, the achievement of SVR according to the stage of liver disease (patients without cirrhosis or with advanced liver disease). The discrepancies between these reviewers were resolved with discussion. The corresponding author was contacted via email if the data presentation was incomplete or if it

was necessary to resolve an apparent conflict or inconsistency in the article.

Statistical analysis

We estimated the SVR rate of velpatasvir plus sofosbuvir combination, in anti-HCV/HCV RNA positive subjects without cirrhosis and advanced fibrosis and naïve to Interferon-free regimen, based on data from all eligible studies together with 95% confidence intervals (CIs).

Statistical heterogeneity between studies included in the meta-analysis was assessed using the Cochran Q test, and the proportion of total variation in study estimates due to heterogeneity was quantified with the I^2 statistic. I^2values between 25% and 49% indicated low heterogeneity, between 50% and 75% indicated moderate heterogeneity and an I^2 value of 75% or above indicated high heterogeneity (4). For heterogeneity, a threshold p value less than 0.1 was considered statistically significant. The Mantel-Haenszel method for a fixed-effects model was applied in the absence of heterogeneity between the studies (Q-statistic: p>0.1 and I^2< 50%) (5), otherwise, the DerSimonian and Laird method for a random-effects model was used if substantial heterogeneity was detected (Q-statistic: p<0.1 or I^2>50%) (6). Subgroup analyses were additionally conducted based on the type of study enrolled (clinical studies vs. real-world studies) and HCV genotype (HCV genotype 1 or 2 or 3 r 6). Potential publication bias was assessed by visual inspections of the Begg funnel plots (6). A two-tailed p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using Stata/IC, version 15.1 software (Stata Corporation, College Station, TX, USA).

Ethics Statement

Approval for the specific study was not required. However, all procedures used in the study were in accordance with the current international guidelines, with the standards on human experimentation of the Ethics Committee of the Azienda Ospedaliera of the University of Campania, Italy, and with the Helsinki Declaration of 1975, revised in 1983.

Results

Literature search

Figure 1 shows a flow diagram of the process of identification and selection of the articles included in the meta-analysis. A total of 1,103 potentially relevant articles were identified from the search of electronic databases. Of these, 1,050 articles were excluded after the first screening based on the title and abstracts, 53 were considered potentially valuable and full texts were retrieved for detailed evaluation. After further evaluation and manual search of the bibliography references of the relevant publications, a total of 16 articles met (7-22) the inclusion criteria and were included in this meta-analysis.

Study characteristics

The main characteristics of the 16 studies included in the meta-analysis are summarized in Table 1; 12 studies (8-12, 16-22) enrolled evaluated the SVR only in subjects without cirrhosis, 4 (7, 13, 14, 15) evaluated the SVR both in subjects without advanced liver disease and in those without cirrhosis. The number of patients per study ranged from 21 to 3,721 subjects, with a total of 6,453 subjects enrolled: 4,907 patients meet inclusion criteria for the definition of "patients without cirrhosis" and 1,371 patients meet the criteria for the definition of "patients without advanced fibrosis".

All the 6,453 patients enrolled were treated with sofosvuvir (400 mg/die) plus velpatasvir (100 mg/die)

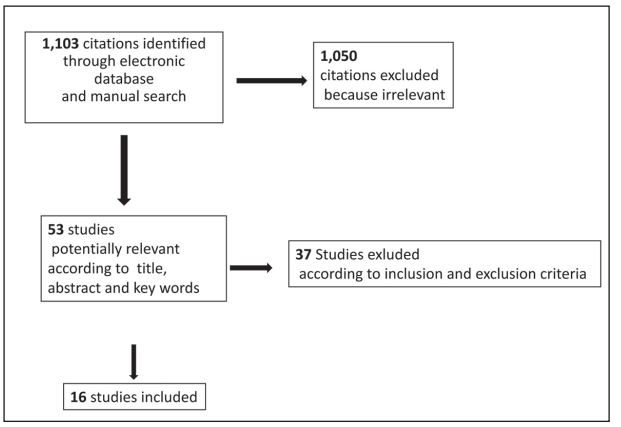

Figure 1. Flow-chart of article selection

Table 1. Characteristic of studies included in the meta analysis

First Author, year [Reference No.]	Country	Type of Study	No. of Patients	Age, mean (SD)	Males (%)	n° (%) with HCV genotype 1a, 1b, 2, 3, 4, 5, 6	Methods for liver fibrosis	N° SVR/pts without cirrhosis	N° SVR/pts without advanced fibrosis
Belpiero, 2019 (7)	USA	Real-word study	3,792	GT2: 62.9 (8.1) VEL/SOF; 63.4 (6.4) VEL/SOF+RIBA; GT3: 56.9 (10.9) VEL/SOF, 61 (6.7) VEL/SOF+RIBA	2273(96) GT2 VEL/SOF, 252 (98.4) GT2 VEL/SOF+RIBA;1360 (95.5) GT3 VEL/SOF, 442 (97.1) GT3 VEL/SOF+RIBA	2939 (51) HCV genotype 2; 2824 (49) HCV genotype 3	FIB-4	2,707/2,881^	1,071/1,134°
Von Felden, 2017 (8)	Germany	Real-word study	293	48(18-77)£	205(70)	293(100)	Liver histology, APRI, TE	158/163^^	Not reported
Wyles, 2017* (9)	USA	Open-label study	106	54(25-72)£	91(86)	66(63) HCV genotype 1a, 12(11) HCV genotype 1b, 11(10) HCV genotype 2, 12(11) HCV genotype 3, 5(5) HCV genotype 4	liver histology, TE, FibroTest, APRI.	82/87	Not reported
Hu, 2018 (10)	China	Real-word study	31	42.7(15.2)	12(39)	12(38.7) HCV genotype 1b, 6(19.4) HCV genotype 2a, 5(16.1) HCV genotype 3a, 5(16.1) HCV genotype 3b, 3(9.7) HCV genotype 6a	Not reported	21/21	Not reported
Gayan, 2018** (11)	USA	Real-word study	78	60.7(28-94)£	53(67.9)	60(76.9) HCV genotype 1a, 18(23.1) genotype 1b	Fibrosure score, liver histology	68/69	Not reported
Isakov, 2018 (12)	Russia, Sweden	Open-label study	119	44(18-71)£	50(50)	8 (7) HCV genotype 1a, 70 (59) HCV genotype 1b, 7 (6) HCV genotype 2, 34 (29) HCV genotype 3	Liver histology, TE, Fibro-test, APRI	96/97	Not reported
Grebely, 2018*** (13)	Australia, Canada, New Zeland, Norway, Switzerland, United Kingdom	Open-label study	103	48(41-43)#	74(72)	35 (34) HCV genotype 1a, 1 (1) HCV genotype 1b, 5 (5) HCV genotype 2, 60 (58) HCV genotype 3, 2 (2) HCV genotype 4	TE	82/86	57/59°°

Table 1. *(Continued)* Characteristic of studies included in the meta analysis

Liu, 2018**** (14)	Taiwan	Real-word study	228	60 (12) no HIV-subjects; 40(10) in HIV-subjects	70(44.0) no HIV-patients; 67(97.1) in HIV subjects	21 (9) HCV genotype 1a, 92 (40) HCV genotype 1b, 89 (39) HCV genotype 2, 7 (3) HCV genotype 3, 3 (1) HCV genotype 4, 16 (7) HCV genotype 6	TE	171/175	144/148°
Nguyen, 2019 (15)	USA	Real-word study	43	65.6(9.8)	19(44.2)	43(100) HCV genotype 6	Liver histology, Fibrotest, TE	38/38	30/30°
Wei, 2018 (16)	China, Thailand, Vietnam, Malaysia, Singapore	Open-label study	375	45(36-54) £	197(53)	22 (6)HCV genotype 1a, 107 (29) HCV genotype 1b, 64 (17) HCV genotype 2, 84 (22) HCV genotype 3, 98 (26) HCV genotype 6	Liver histology, Fibrotest, TE	302/308	Not reported
Wu, 2019 (17)	China	Open-label study	23	41(25-76) £	16(26.67)	23(100) HCV genotype 6	APRI, TE, FIB-4	23/23	Not reported
Sood, 2019 (18)	India	Open-label study	129	42(19-75) £	76(59)	6 (5) HCV genotype 1a, 22 (17) HCV genotype 1b, 90 (70) HCV genotype 3, 7 (5) HCV genotype 4, 1 (1) HCV genotype 6	Not specified	79/87^^^	Not reported
Tao, 2018 (19)	China	Cohort study	21	37 (33.10-41.67)	13(62)	21 (100) HCV genotype 3	TE	16/16	Not reported
Everson, 2015 (20)	USA	RCT	77	Genotype 1 49 (20-68) £, Genotype 3 50 (20-70) £, Genotype 4-6 54 (23-70) £	Genotype 1 17 (61), Genotype 3 17 (63), Genotype 4-6 15 (68)	28 (36) HCV genotype 1, 27 (35) HCV genotype 3, 22 (29) HCV genotype 4-6	Liver hisology, TE, APRI, FibroTest	74/77	Not reported
Feld, 2015 (21)	USA, Canada, Europe, Hong Kong	RCT	624	54 (18-82) £	374(60)	210 (34) HCV genotype 1a, 118 (19) HCV genotype 1b, 104 (17) HCV genotype 2, 116 (19) HCV genotype 4, 35 (6) HCV genotype 5, 41 (7) HCV genotype 6	Liver hostology, FibroTest, TE	496/501^^^^	Not reported
Foster 2015 (22)	USA, Canada, Europe	RCT	413	Genotype 2 57(26-81) £, Genotype 3 49(21-76) £	Genotype 2 86(64), Genotype 3 170(61)	134 (33) HCV genotype 2, 277 (67) HCV genotype 3	Liver histology, FibroTest, TE, APRI	274/278	Not reported

TE: transient elastography, RCT: randomized controlled study; £ mean (range), # median(IQR); *: in HIV-subjects; **: in Africa-American subjects; ***: in PWID; ****: 68 HIV-subjects; ^: 56 patients with a previous failure to Interferon-free regimen ; ^^: 5 patients with a previous failure to Interferon-free regimen ^^^: 1 patient with a failure to previous Interferon-free regimen; ^^^^: 23 patients with failure to previous Interferon-free regimen; °: patients with F0-F2 fibrosis score °°: patients with F0-F1 fibrosis score

for 12 weeks without ribavirin, except 54 patients in which ribavirin has been used (8).

All patients were naive to previous antiviral treatment, except 56 patients in the Belpiero study (7), 5 in Von Felden study (8), 1 in Sood study (18) and 23 in Feld study (21) who were previously treated with Interferon-free regimen. One study (9) enrolled only anti-HIV-positive patients, and one (11) only African-American subjects.

Considering the type of the studies, 7 were real-world studies (7, 8,10, 11, 14, 15, 19) and 9 clinical studies, specifically 6, were open-labelled trial (9, 12, 13, 16, 17, 18) and 3 randomized controlled trials (20-22) (RCTs).

Meta-analyses of the data

The results of the meta-analysis for the estimated prevalence of SVR are shown in Table 2. Considering all the 4,907 subjects without cirrhosis included in the 16 studies enrolled (7-22), the prevalence of SVR by a 12-week sofosbuvir plus velpatasvir-regimen was 98% (95% CI: 96-99%) (Table 2 and Figure 2). The prevalence of SVR was similar considering the 1,532 subjects from the 9 clinical studies (9, 12, 13, 16, 17, 18,

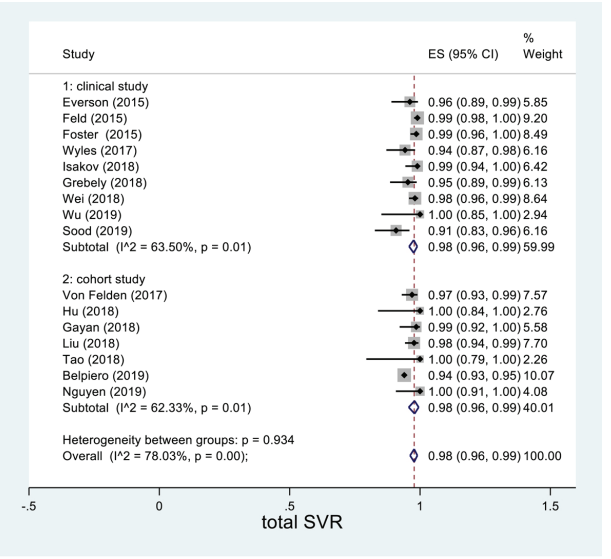

Figure 2. Meta-analysis of the prevalence of SVR in subjects without cirrhosis according to type of study

Table 2. Summary of meta-analysis results in the achievement of the sustained virological response by velpatasvir plus sofosbuvir in naïve patients with chronic hepatitis C and mild fibrosis

	N° of studies	N° of patients	N° of subjects with SVR	Summary of SVR prevalences (%)	95% CI (%)	Heterogeneity test (I^2%; p)
All subjects without cirrhosis	16 (7-21)	4,907	4,687	98	96-99	78; <0.0001
- In clinical studies	9 (9, 12, 13, 16, 17, 18, 20-22)	1,544	1508	98	97-99	63; 0.01
- In real-world studies	7 (7, 8, 10, 11, 14, 15, 19)	3,363	3179	98	96-99	62; 0.01
- with genotype 1	3 (11. 20, 21)	352	347	99	97-100	0; 0.9
- With genotype 2	2 (7, 21)	1,940	1,836	95	94-96	0; NR
- With genotype 3	6 (7, 8, 17, 19, 20, 22)	1,431	1,348	96	93-99	61.47; 0.02
- With genotype 6	3 (15, 17, 21)	96	96	100	98-100	0; 0.98
All subjects without advanced fibrosis	4 (7, 13, 14, 15)	1,371	1,302	96	94-98	35.81; 0.20

20-22) and the 3,363 subjects from the 7 real-world studies (7, 8, 10, 11, 14, 15, 19) (98%, CI 95%: 96-99% and 98%; CI 95%: 96-99%, respectively).

Similarly, considering the 4 studies (7, 13, 14, 15) enrolling 1,371 subjects without advanced liver fibrosis the prevalence of SVR was 96% (95% CI: 94-98%) (Table 2 and Figure 3).

Table 2 and Figures 3-6 show the prevalence of SVR considering HCV genotype stratification. Data indicate a prevalence of SVR of 99% (95% CI: 97-100%) in the 3 studies (11, 20, 21) enrolling 352 patients with HCV genotype 1 (Figure 4), of 95% (95% CI: 94-96%) in the 2 studies (7, 21) enrolling 1,940 patients with HCV genotype 2 (Figure 5), of 96% (95% CI: 93-99%) in the 6 studies (7, 8, 17, 19, 20, 22) enrolling 1,431 patients with HCV genotype 3 (Figure 6) and 100% (95% CI: 98-100%) in the 3 studies (15, 17, 21) enrolling 96 patients with HCV genotype 6 (Figure 7).

Heterogeneity was calculated among all studies using the I^2 test. As shown in Table 2, heterogeneity was found in all meta-analyses except for the meta-analyses in patients without cirrhosis and with genotype 1 or 2 or 6 and in those without advanced fibrosis (Table 2).

Visual inspection of the funnel plots and Egger's tests were performed to assess the potential publication bias of the studies included in this meta-analysis.

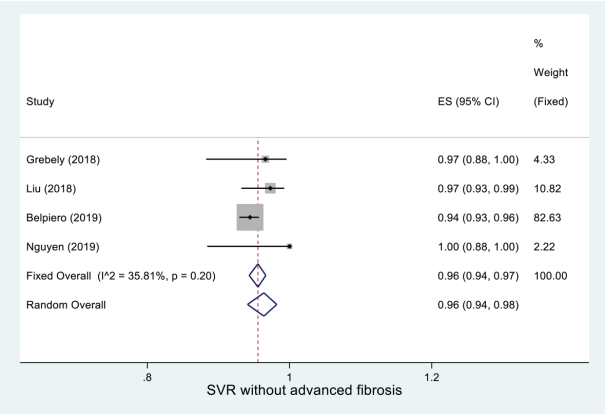

Figure 3. Meta-analysis of the prevalence of SVR in subjects without advanced fibrosis (F0-F2)

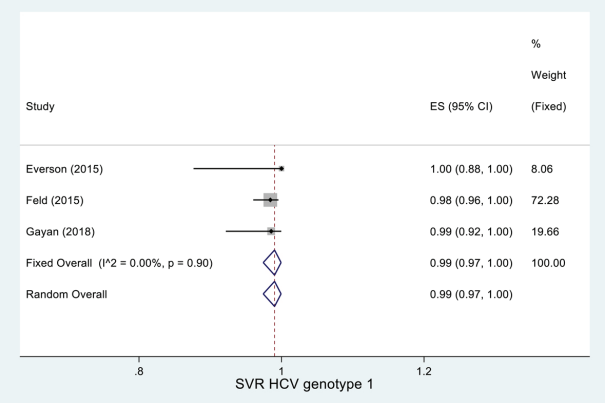

Figure 4. Meta-analysis of the prevalence of SVR in HCV genotype-1 subjects without cirrhosis

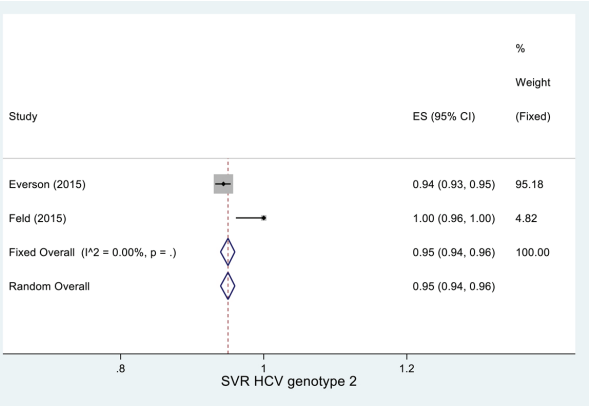

Figure 5. Meta-analysis of the prevalence of SVR in HCV genotype-2 subjects without cirrhosis

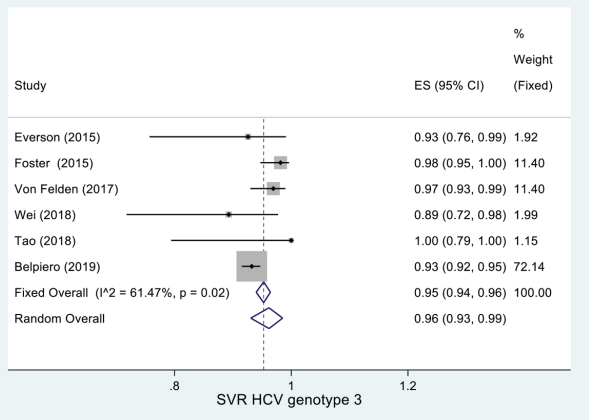

Figure 6. Meta-analysis of the prevalence of SVR in HCV genotype-3 subjects without cirrhosis

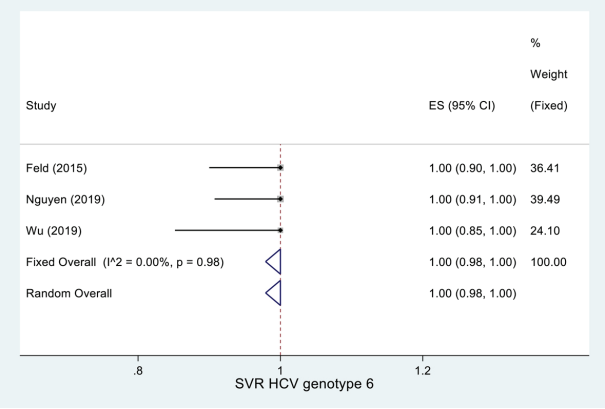

Figure 7. Meta-analysis of the prevalence of SVR in HCV genotype-6 subjects without cirrhosis

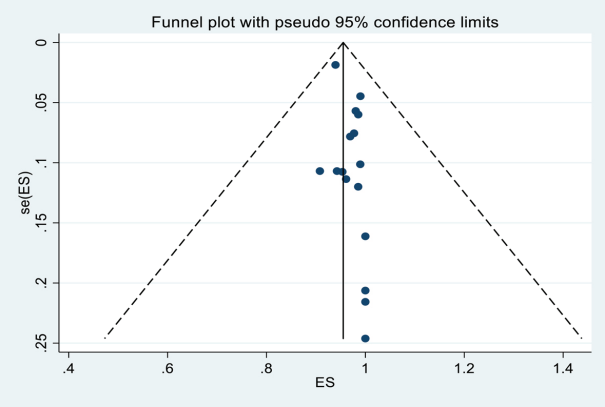

Figure 8. Funnel plot of the risk ratios vs. the reciprocal of their standard errors of all studies included in the meta-analysis

The shapes of the funnel plots did not reveal any clear evidence of obvious asymmetry in the analysis of the whole study (Figure 8). The Egger test results showed no significant statistical evidence of publication bias in the analysis of all studies included, which indicated a low risk of publication bias.

Discussion

The sofosbuvir plus velpatasvir combination is a powerful pan-genotypic regimen with a high genetic barrier against the emergence of resistance associated substitution (RAS) and consequently with high level of SVR regardless HCV genotypes. Moreover, this combination has an optimal safety profile, even for difficult-to-treat patients such as decompensated cirrhotic subjects (2, 3). However, few data are available in literature for patients with initial fibrosis, especially from real-word experiences.

Data of our meta-analysis analyzed in naïve patients with chronic HCV infection and mild fibrosis the efficacy of the single-tablet regimen of sofosbuvir plus velpatasvir without ribavirin, showing that it is highly effective in chronic HCV patients without cirrhosis (SVR12 rate = 98%) and in HCV patients without advanced liver fibrosis (SVR12 rate = 96%). Furthermore, it is of great interest to note that according to our study the prevalence of SVR was similar considering both clinical trials and real-world studies (98%, CI 95%: 96-99% and 98%; CI 95%: 96-99%, respectively). Therefore, a 12-week sofosbuvir plus velpatasvir-regimen is suitable for all stages of liver disease, as well demonstrated both by the data present in literature and by the correspondence between the results of clinical studies and real-life studies. The clarification that the rate of SVR was very high also in subjects with initial fibrosis and in real-word studies seems to be important, also considering that today most of HCV subjects starting DAA-regimen has not advanced liver fibrosis (24, 25).

Evaluating the stratification of the data according to the different HCV genotypes, the prevalence of SVR is high ranging to 95-100% also in HCV genotypes difficult-to-treat such as genotypes 1, 3 and 6 with a prevalence of SVR of 99%, 96% and 100% respectively, confirming international literature on this topics. Thus, Sofosbuvir plus velpatasvir regimen makes HCV treatment easier as the same therapy schedule are suitable for all the genotypes, irrespective of the fibrosis stage, making it a pangenotypic and panfibrotic regimen. Moreover, the single-pill, once-a-day posology improves the adherence to the therapy and the absence of lactose and gluten make it suitable to patients intolerant or allergic to these substances. Considering also the minimal drug-drug-interactions, this regimen may be consider a standard of care for the treatment of chronic HCV infection.

This meta-analysis has several strengths. First, a comprehensive literature search strategy was applied to minimize identification and selection bias and many

studies were identified as evaluating the prevalence of SVR in naïve subjects with chronic HCV infection without advanced fibrosis treated with sofosbuvir plus velpatasvir without ribavirin for 12-weeks. Second, the extensive amount of data reviewed. Third, in the present meta-analysis no between-study heterogeneity was observed. Heterogeneity is a potential problem when interpreting the results of all meta-analyses and finding the sources of heterogeneity is one of the most important goals.

However, there are some limitations which should be addressed when interpreting the findings of this meta-analysis. First, the findings are in part based on the results of observational studies and, therefore, as in observational studies themselves, recall and selection biases cannot be ruled out, and it is not possible to exclude potential confounding by various variables associated with exposure. Second, we did not search for unpublished studies, and this meta-analysis included only studies which were published in English and, as in any meta-analysis of published data, a publication bias may have occurred because small studies with null results tend not to be published, but there was no statistical evidence of a non-publication bias from the visualization of the funnel plot or from Egger's test.

Conclusion

Sofosbuvir plus velpatasvir therapeutic regimen was highly effective in HCV patients without advanced liver disease naïve to previous DAA regimen regardless the different HCV genotypes. Also considering that this combination is highly safe with a very low rate of severe adverse event such as identified both in clinical and real-word studies (7, 14, 19-22), it can therefore be considered a therapeutic regimen adaptable to all stages of liver disease and could be considered as well pan-genotypic as pan-fibrotic regime, confirmed not only by clinical trials but also by real life studies.

Author Contributions: MP was responsible for the conception and design of the study, assessed the quality of the studies, analysed the data and wrote the manuscript; AR: performed the literature search and data extraction; LO participated in the conception of the study, performed the literature search, data extraction, and assessed the quality; NC was responsible for the conception and design of the study, interpreted the data and wrote the manuscript. All authors read and approved the final manuscript

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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