CLINICAL INVESTIGATION

Sofosbuvir for the treatment of patients with genotype 2 or 3 chronic hepatitis C virus infection

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Treatment of chronic hepatitis C will dramatically change with the introduction of direct antiviral agents that allow interferon-free treatment schedules. However, most of the currently developed direct antiviral agents focus on genotype 1. Thus, other genotypes, especially genotype 3 will become more difficult to treat with interferon-free regimens in the near future in comparison with genotype 1. Hepatitis C virus genotype 3 may convert to the most problematic genotype as not only interferon-free therapies are more challenging but also progression to cirrhosis is faster. Sofosbuvir, a NS5B nucleoside HCV polymerase inhibitor is one of the direct antiviral agents that has pan-genotypic efficacy. Phase III trials investigating sofosbuvir plus ribavirin treatment in patients with hepatitis C virus genotype 2 and 3 infection have been completed and sofosbuvir was approved by the US FDA and European Medicines Agency.

Keywords: direct acting antivirals • HCV genotype 2 • HCV genotype 3 • HCV RNA • hepatitis C virus • pegylated IFNα • ribavirin • sofosbuvir

Seven major genotypes (G1–G7) have been identified for the hepatitis C virus (HCV), with different distribution across the world [1]. G1 is the most prevalent; however, in some parts of the world, G2 and G3 have significant impact [2]. For example, G2 and G3 are common genotypes in some parts of Asia, with G3 being the dominant genotype in India and Pakistan and G2 in Taiwan [3,4]. Thus, the size of the population of the affected countries and the seroprevalence of HCV G2 and G3 lead to a significant total number of HCV G2- and G3-infected people in need of therapy. Although HCV G2 and G3 are often evaluated together, major differences exist between their natural course and response to treatment.

G3 has a faster progression to cirrhosis and patients who failed to achieve sustained virological response (SVR; negative results for HCV RNA 12 or 24 weeks after end of treatment) have an increased mortality in comparison with G1 and G2 [5,6]. Infection with HCV G3 even outweighs alcohol use and diabetes mellitus as a risk factor for mortality, as shown by a large study by van der Meer and colleagues [7]. Fortunately, successful therapy lowers the increased risk of mortality in HCV G3 to the same risk level of the other genotypes [6]. G3 is also linked to higher rates of liver steatosis. Due to the correlation with HCV RNA, it is considered to be virus-induced steatosis. Viral eradication subsequently leads to a decline in steatosis [8,9].

In consideration of the increased mortality and faster progression to cirrhosis, a distinct urge for treatment exists in HCV G3. Even more so, as successful therapy can negate most of the detrimental effects.

The current standard of care (SOC) for HCV G2 and G3 infection is based on pegylated interferon alpha (PEG-IFN) and ribavirin (RBV) [10]. Different results for SVR are described in the literature and significant distinctions in favour of HCV G2 are reported; that is, Zeuzem *et al.*, who reported SVR rates of 93% in HCV G2 and 79% in HCV G3 [11]. A meta-analysis by Andriulli *et al.* confirmed the favourable

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findings for HCV G2, albeit their study stated lower SVR rates with an overall SVR rate of 74% for G2 and 68% for G3 [12].

In summary, the natural course of HCV G2 and G3 is different, with a faster progression and higher mortality linked to HCV G3. Despite the bigger need for therapy, HCV G3 has lower response rates to current PEG-IFN/RBV therapy

To spare side effects and increase response rates, several studies compared different treatment durations to increase the treatment efficacy. Although a fixed duration of 24 weeks has been proposed [13], response-guided therapy has been found to have an optimized risk–benefit ratio. Based on rapid virological response (RVR; undetectable HCV RNA after 4 weeks of treatment), early virological response (EVR; undetectable HCV RNA after 12 weeks of treatment) and risk factors for treatment failure, therapy duration varies between 16 and 48 weeks [10,14]. As mentioned, for both genotypes the most important predictor for successful therapy and, therefore, the most important factor for response-guided treatment, is the RVR. RVR can be achieved in 62–78% of G2 and G3 patients, however sensitive assays should be used to test for HCV RNA [15–18]. Though reduction of treatment to less than 24 weeks increased the chance of relapse [18,19], shortening is an option to spare side effects and costs in selected patients [14]. A treatment duration of 12–16 weeks is possible in patients who show RVR defined by HCV RNA negativity with a sensitive HCV assay by week 4 of therapy [16–17,20]. Though it is important to note that the dose of RBV should not be given as flat dose of 800 mg in response-guided therapy regimens [14]. Several risk factors for poor SVR rates have been identified that should not allow response-guided treatment: baseline viral load, immunosuppression, advanced cirrhosis, age, adipositas, and nonadherence to therapy [16,21–23]. The predictive value for IL28b is less for G2 and G3 compared with G1 [23]. However, despite the huge efforts that have been made to understand and optimize the therapy for HCV G2 and G3, the treatment has basically not changed in recent years and the compounds PEG-IFN and RBV, with their specific drawbacks, remained the mainstay of therapy.

Considering the higher mortality and the lower response rates to treatment of HCV G3, a huge need exists for new therapies. This is even more important in hard-to-treat patients, who are defined by a combination of HCV G3, cirrhosis, high baseline viral load, age, adipositas and non-compliance. Furthermore, no treatment options exist for patients who are not eligible for PEG-IFN treatment or who did not respond to SOC.

A small improvement was achieved in 2011 with the approval of the first two direct-acting antivirals (DAA). Boceprevir (BOC) and telaprevir (TLV) are both HCV protease inhibitors (PI) that still require the combination of PEG-IFN and RBV. However, both PIs are only approved for G1. Nevertheless, some patients with G2 and G3 have been exposed to BOC and TLV. The combination of TLV, PEG-IFN and RBV did show an increased antiviral activity in G2 in comparison with only PEG-IFN and RBV, whereas no additional benefit could be observed in G3 [24].

In comparison, BOC showed some antiviral activity in both, G2 and G3. However, only the dose of 400 mg t.i.d. has been studied and not the approved dose of 800 mg t.i.d. [25]. Based on these data, BOC and TLV cannot be recommended for non-G1 patients.

Most of the other DAAs that are currently investigated in Phase II–III trials have limited efficacy in HCV G2 and G3. Some PIs like simeprevir, asunaprevir, faldaprevir and MK 5172 showed an effect in HCV G2, but no effect or only a reduced effect (i.e., MK 5172 in higher doses) in HCV G3. The NS5A inhibitor daclatasvir as well as the combination of the PI ABT-450/r and the NS5A inhibitor ABT-267 have been tested successfully in HCV G2 and G3. Though, HCV G2 showed better response rates for both treatment regimens [26–31]. More data for these DAA are needed to judge their use in HCV G2 and G3. Non-nucleosides did not show an effect [32].

However, nucleoside polymerase inhibitors have pan-genotypic efficacy. Sofosbuvir (SOF, Gilead Sciences) is the most advanced NS5B polymerase inhibitor and will be evaluated in more detail in the following section.

Besides DAA, host-targeting antivirals may also play a role in further treatment regimens. The host-targeting antiviral alisporivir, which is a cyclophillin A inhibitor has been shown to be effective in HCV G2 and G3 [33,34]. Of note, alisporivir demonstrated best results in HCV G3 in a trial with HCV/HIV co-infected patients with G1, G3 and G4 [35].

SOF in the treatment of HCV G2 & G3

As already mentioned, there is a huge need for new treatment options in HCV G2 and G3, especially in regard of interferon-free treatment. This need could potentially be addressed by SOF, a new NS5B-polymerase inhibitor. NS5B is an HCV RNA dependent RNA polymerase and essential for viral replication.

Amazing results have been shown in the first trial, which has evaluated the combination of SOF, RBV and PEG-IFN (added for 4–12 weeks) and even SOF and RBV without PEG-IFN. This trial has demonstrated 100% SVR [36]. Monotherapy with SOF has been also tested in ten patients but SVR was only 60%, rendering RBV still irreplaceable in current HCV therapy.

Table 1. Baseline characteristics and study regimen for Phase III trials with sofosbuvir in hepatitis C virus genotype 2/3.

Subgroup	FISSION		POSITRON		FUSION	
	PEG-IFN 180 µg/w + RBV 800mg/d	SOF 400 mg/d + RBV 1000–1200 mg/d	SOF 400 mg/d + RBV 1000–1200 mg/d	Placebo	SOF 400 mg/d + RBV 1000–1200 mg/d	SOF 400 mg/d + RBV 1000–1200 mg/d
Treatment duration (weeks)	24	12	12	12	12	16
Received treatment (n)	243	256†	207	71	103	98
Discontinued treatment (n)	54	11	6	3	1	0
Completed treatment (n)	189	245	201	68	102	98
Returned for SVR12 (n)	225	239	171	71	54	73
Male sex (n; %)	156 (64)	171 (76)	117 (57)	34 (48)	73 (71)	67 (68)
G2 (n; %)	67 (28)	70 (27)	109 (53)	34 (48)	36 (35)	32 (33)
G3 (n; %)	176 (72)	183 (71)	98 (47)	37 (52)	64 (62)	63 (64)
HCV RNA ≥800,000 IU/ml (n; %)	157 (65)	145 (57)	150 (72)	55 (77)	80 (78)	77 (79)
IL28B						
CC (n; %)	106 (44)	108 (42)	97 (47)	29 (41)	31 (30)	30 (31)
CT (n; %)	98 (40)	121 (47)	84 (41)	36 (51)	53 (51)	56 (57)
TT (n; %)	38 (16)	25 (10)	26 (13)	6 (8)	19 (18)	12 (12)
Cirrhosis (n; %)	50 (21)	50 (20)	31 (15)	13 (18)	36 (35)	32 (33)
Baseline ALT > 1.5 ULN (n; %)	146 (60)	138 (54)	117 (57)	42 (59)	63 (61)	56 (57)
Interferon classification						
Contraindication (n; %)	n.a.	n.a.	88 (43)	33 (46)	n.a.	n.a.
Unacceptable side effects (n; %)	n.a.	n.a.	17 (8)	8 (11)	n.a.	n.a.
Patients decision (n; %)	n.a.	n.a.	102 (49)	30 (42)	n.a.	n.a.
Response to previous treatment						
Nonreponse (n; %)	n.a.	n.a.	2 (3)	2 (1)	25 (24)	25 (26)
Relapse (n; %)	n.a.	n.a.	4 (6)	11 (5)	78 (76)	73 (74)

†Three patients with G1 were excluded from analysis.
/d: Daily; G: Genotype; n.a.: Not applicable; RBV: Ribavirin; SOF: Sofosbuvir; /w: Weekly.
Adapted from [38,39].

SOF & ribavirin in comparison with the current SOC

The efficacy of the SOF and RBV combination was studied in further trials. Although these larger studies were not able to reproduce the extraordinary results by Gane *et al.*, they proved the efficacy of SOF and RBV in HCV G2 and G3. The FISSION-trial in treatment-naive patients compared the 'old' SOC; 24 weeks of PEG-IFN and 800 mg RBV with 12 weeks of SOF and 1000–1200 mg RBV. The primary outcome was to assess if SOF and RBV is safe and noninferior to PEG-IFN and RBV, based on SVR12 [37]. In total, 527 patients were randomized; 256 patients received treatment in the SOF/RBV cohort and 243 patients in the

PEG-IFN/RBV cohort. In both groups, 50 patients had cirrhosis (20–21%). 71–72% of the patients were G3 and 27–28% were G2 infected. IL28B genotype CC was represented in 42-44% of patients (Table 1). Of note, three of the patients in the SOF/RBV arm were found to be G1 infected and excluded from further analysis.

The SVR12 for both cohorts was 67%, demonstrating no difference between therapy with SOF/RBV and PEG-IFN/RBV in the overall analysis. However, the subgroup analysis revealed superior results for SOF/RBV in HCV G2 patients. These patients showed a SVR of 97% with SOF/RBV, whereas PEG-IFN/RBV demonstrated a SVR of 77.6% (Table 2). In HCV G3 PEG-IFN/RBV had a slightly better response with SVR rates of 63% in comparison with SOF/RBV with 56%.

For both treatment arms, a further decline of SVR was observed in cirrhotic patients. For SOF/RBV the SVR was 47% and 38% for PEG-IFN/RBV (Table 2).

Thus, the overall response rates in cirrhotic patients favoured SOF/RBV. However, in HCV G3 patients with HCV RNA < 6 $\log^{10}$ IU/ml PEG-IFN/RBV was superior, irrespective of the cirrhosis status. Even more, PEG-IFN showed a considerably higher SVR in patients < 50 years of age, whereas in all other Phase III trials SOF/RBV favoured patients > 50 years of age (Table 2).

Several cofactors for treatment success have been analyzed. No major difference in SVR could be demonstrated for body mass index or baseline alanine transaminase between SOF/RBV and PEG-IFN/RBV; however, body mass index > 30 and baseline alanine transaminase > 1.5 ULN are associated with slightly lower treatment responses for both treatments. For SOF/RBV only a small difference for IL28B CC and non-CC genotype could be found with 69.8% for IL28B CC and 66.2% for IL28B non-CC, in opposition to PEG-IFN/RBV, which is more heavily influenced by IL28B genotype. Overall, HCV G3, male gender, cirrhosis and baseline HCV RNA > 6 $\log^{10}$ IU/ml were associated with a poorer treatment response for both treatment concepts (Table 2). Thus, difficult to treat patients remain difficult to treat with SOF/RBV for 12 weeks.

Despite similar SVR12 of 67%, the adverse events (AE) profile and treatment duration favoured SOF/RBV over PEG-IFN/RBV (Table 3). In the PEG-IFN/RBV arm, 54 patients discontinued treatment, 26 due to AEs and 17 due to viral failure. In contrast, only 11 patients in the SOF/RBV arm discontinued treatment, three due to AEs and one due to viral failure.

Furthermore, the analysis of proportional differences of frequent AEs that occurred in more than 10% of patients favoured SOF/RBV over PEG-IFN/RBV. As expected, highly significant differences could be found for typical side effects of PEG-IFN treatment, while a non-significant trend could be documented for dizziness, irritability and anemia. The most common side effects, affecting at least 10% a patients in a study arm, are depicted in Table 3.

Hematologic abnormalities regarding hemoglobin occurred in both treatment groups, but a drop below a hemoglobin value of <10 g/dl was slightly more frequent in the PEG-IFN/RBV arm in comparison with the SOF/RBV arm. A drop below hemoglobin 8.5 g/dl occurred in 2% of the PEG-IFN/RBV patients and in less than 1% in the SOF/RBV treated patients, although absolute numbers were small, with four patients versus one patient. Reduction of neutrophils, platelets and white blood cell count only occurred in the PEG-IFN/RBV treated patients and no major deviation could be documented for SOF/RBV. As a hemoglobin drop below 10 g/dl is often accompanied by the need of blood transfusions, hospitalization, treatment modification or discontinuation in selected patients; that is, patients with cardiac diseases, the lesser frequency of hematologic abnormalities is an advantage of the SOF/RBV therapy.

AEs have always been of concern in treatment decisions with PEG-IFN/RBV, especially in cirrhotic patients. Therefore, next to overall safety, the rate of AEs between the cirrhotic and the non-cirrhotic patients within the SOF/RBV arm are of special interest. No differences for treatment associated AE between the cirrhotic and non-cirrhotic patients could be demonstrated (Table 3). In contrast, in cirrhotic patients the rates of any grade 3 and serious AEs had been 12% (n = 6) and 4% (n = 2), respectively. These numbers are twice as high in comparison to the non-cirrhotic patients. This data may represent the fact that cirrhotic patients have overall higher risks than non-cirrhotic patients due to their underlying condition, but suggests that SOF/RBV treatment does no increase the risk of AEs. However, because of the small absolute numbers, this data should be interpreted carefully and further monitoring of cirrhotic patients under treatment is warranted. Far advanced cirrhotic patients have not been included in this trial and other trials with PEG-IFN based therapies in real-life cohorts have shown severe AEs in patients with advanced cirrhosis [40].

Of note, 74 patients relapsed after treatment with SOF/RBV and deep sequencing was performed to investigate resistance. No mutation associated with SOF was found in NS5B and no decreased susceptibility was observed.

In summary, the combination of SOF and RBV proved to be superior over the current SOC in consideration of treatment duration, side effects and treatment success in HCV G2.

SOF & RBV in interferon-intolerant & treatment-experienced patients

The biggest need for new therapies is seen in patients who failed to respond to previous PEG-IFN/RBV or who were not eligible for interferon-based treatment. Furthermore, efficacy and safety of longer treatment duration in these hard-to-treat patients is of special interest. These needs were investigated in the POSITRON and FUSION studies [41].

The POSITRON study included 207 patients who were not eligible or intolerant for PEG-IFN treatment and received treatment with SOF/RBV (Table 1). They were compared with a placebo group, consisting of 71 patients. The most common reasons for PEG-

Table 2. SVR12 in Phase III trials with sofosbuvir in hepatitis C virus genotype 2/3.

Subgroup	FISSION		POSITRON		FUSION	
	PEG-IFN/RBV 24 weeks	SOF/RBV 12 weeks	SOF/RBV 12 weeks	Placebo 12 weeks	SOF/RBV 12 weeks	SPF/RBV 16 weeks
Overall SVR12 (ITT)	162/243 (66.7)	170/253 (67.2)	161/207 (77.8)	0/71 (0)	50/100 (50)	69/95 (73)
Age at baseline						
< 50 years	86/118 (72.9)	80/126 (63.5)	53/72 (73.6)	0/20 (0)	9/21 (42.9)	16/23 (69.6)
> 50 years	76/125 (60.8)	90/127 (70.9)	108/135 (80)	0/51 (0)	41/79 (51.9)	53/72 (73.6)
Gender						
Male	96/156 (61.5)	103/168(61.3)	85/117 (72.6)	0/34 (0)	30/71(42.3)	42/64 (65.6)
Female	66/87 (75.9)	67/85 (78.8)	67/85 (78.8)	0/37 (0)	20/29 (69.0)	27/31 (87.1)
Cirrhosis						
No	143/193 (74.1)	147/204 (72.1)	142/176 (80.7)	0/58 (0)	39/64 (60.9)	48/63 (76.2)
Yes	19/50 (38.0)	23/49 (46.9)	19/31 (61.3)	0/13 (0)	11/36 (30.6)	21/32 (65.6)
HCV G/cirrhosis						
G2 overall	52/67 (77.6)	68/70 (97.1)	101/109 (93)	0/34 (0)	31/36 (86.1)	30/32 (93.8)
G2 cirrhosis	n.a.	n.a.	16/17 (94)	n.a.	6/10 (60.0)	7/9 (77.8)
G2 no cirrhosis	n.a.	n.a.	85/92 (92)	n.a.	25/26 (96.2)	23/23 (100)
G3 overall	110/176 (62.5)	102/183 (55.7)	85/92 (92)	0/37 (0)	19/64 (29.7)	39/63 (61.9)
G3 cirrhosis	n.a.	n.a.	3/14 (21)	n.a.	5/26 (19.2)	14/23 (60.9)
G3 no cirrhosis	n.a.	n.a.	57/84 (68)	n.a.	14/38 (36.8)	25/40 (62.5)
Baseline HCV RNA						
< 6 $\log^{10}$ IU/ml	71/106 (67.0)	80/107 (74.8)	51/67 (76.1)	0/17 (0)	13/26(50.0)	18/29 (62.1)
> 6 $\log^{10}$ IU/ml	91/137 (66.4)	90/146 (61.6)	110/140 (78.6)	0/54 (0)	37/74 (50.0)	51/66 (77.3)
Baseline BMI						
< 30 kg/m^2	117/172 (68.0)	120/176 (68.2)	103/136 (75.7)	0/49 (0)	39/71 (54.9)	43/61 (70.5)
> 30 kg/m^2	45/71 (63.4)	50/77 (64.9)	58/71 (81.7)	0/22 (0)	11/29 (37.9)	26/34 (76.5)
IL28B						
CC	82/106 (77.4)	74/106 (69.8)	0/49 (0)	39/71 (54.9)	15/30 (50.0)	35/70 (50.0)
Non-CC	79/136 (58.1)	96/145 (66.2)	87/110 (79.1)	0/42 (0)	35/70 (50.0)	50/68 (73.5)
Response to prior HCV treatment						
Nonresponse	n.a.	n.a.	n.a.	n.a.	35/70 (50.0)	16/25 (64.0)
Relapse	n.a.	n.a.	n.a.	n.a.	39/75 (52.0)	53/70 (75.7)

All results are shown as n/total (%).
G: Genotype; HCV: Hepatitis C virus; n.a.: Not available; PEG-IFN: Peginterferon alpha; RBV: Ribavirin; SOF: Sofosbuvir; SVR: Sustained virological response; ITT: Intention-to-treat.
Adapted from [38,39].

IFN ineligibility had been a psychiatric disease in 57% of patients and an autoimmune disorder in 19% of patients. The most common reasons for PEG-IFN intolerance had been flu-like symptoms (32%), psychiatric disease (20%), thrombocytopenia (16%) and local/systemic adverse reaction (12%).

The FUSION-study included 201 patients, who did not respond to prior PEG-IFN/RBV therapy. SOF/RBV for 12 and 16 weeks have been compared in this trial to assess, if treatment prolongation is safe and yields higher SVR rates. Both groups were matched equally in regard of the response to the prior treatment, with 24–26% nonresponders and 74–76% relapsers (Table 1).

The POSITRON study confirmed the good results for HCV G2 patients with a 93% SVR in the overall analysis (Table 2). Cirrhotic patients and non-cirrhotic patients responded equally to the treatment with 94% SVR and 92% SVR, respectively. On the downside, it also confirmed the lower rates of SVR in HCV G3 with 61%. The subgroup of cirrhotic HCV G3 infected patients achieved even lower rates of SVR with 21%, whereas non-cirrhotic patients had a SVR of 68% (Table 2). Male sex, HCV G3 and previous HCV treatment > 12 weeks were significantly associated with a lower chance of SVR.

The FUSION study showed that 16 weeks of SOF/RBV therapy are superior to 12 weeks, especially in difficult-to-treat patients. G3 patients who did not respond to PEG-IFN/RBV previously, achieved SVR rates of 62% with 16 weeks and only 30% SVR with 12 weeks of treatment (Table 2). Patients with liver cirrhosis demonstrated 66% SVR with 16 weeks SOF/RBV versus 31% SVR with 12 weeks (Table 2). Even though treatment for 12 weeks delivered good results of 86% SVR for HCV G2, 16 weeks of treatment raised the response rate to 94% in this patient population. An interesting finding is that the good results in cirrhotic HCV G2 patients from the POSITRON trial with 94% SVR could not be reproduced. The non-cirrhotic G2 patients had a SVR of 96.2% for 12 weeks of treatment and 100% for 16 weeks of treatment, but the cirrhotic G2 patients achieved only 60% for 12 weeks and 77.8% for 16 weeks of treatment (Table 2). However, the number of patients in this subgroup was rather small (Table 2). One reason could be that the number of male participants in the FUSION trial was significantly higher than in the POSITRON trial and SVR in male patients was consistently lower in all Phase III trials of SOF (Table 2).

Comparing the SVR12 in dependence of the response to prior HCV therapy, nonresponse was slightly associated with a lower SVR chance. Though treatment prolongation yielded higher SVR rates for both, non-response and relapse, the gap between the groups was maintained. SVR rates for prior non-response had been 64%, whereas prior relapse showed 75.7% SVR.

The overall rate of AEs leading to discontinuation of treatment in both, POSITRON and FUSION trial, was low with 2.4 and 1%, even below treatment discontinuation in the placebo arm of the POSITRON trial with 4.2% (Table 3). The overall rate of treatment related AEs in the POSITRON trial was 70.5% in the non-cirrhotic patients and 83.9% in the cirrhotic patients. Though, the majority were G1 AEs, no increased rate of serious AEs or G3 AEs could be found for cirrhotic patients in comparison with non-cirrhotic patients with 5.1 versus 6.5% and 29 versus 22.6%, respectively. These findings were mirrored in the FUSION trial. The treatment prolongation to 16 weeks did not led to significantly increased rates of AEs, suggesting that treatment prolongation is a safe option. As in the FISSION trial, SOF/RBV treatment led to a drop in hemoglobin count, but did not significantly decrease white blood cell count, neutrophils or platelets. Treatment prolongation to 16 weeks did not lead to increased hemoglobin abnormalities.

In both the POSITRON and the FUSION trial, 115 patients relapsed after stopping treatment. In 112 patients sequencing could be successfully done. Though in some patients NS5B substitutions were observed, no reduced susceptibility to SOF/RBV could be found.

SOF in hard-to-treat-patients & in combination with other DAA

In direct comparison of the results for G2 and G3 in the aforementioned trials with SOF, G3 had poorer SVR rates. This finding has been addressed by two studies, the results of which were presented recently at the American Association for the Study of Liver Diseases 2013. As treatment prolongation to 16 weeks showed increasing but not yet sufficient SVR rates for G3 in the FUSION trial, the VALENCE trial was amended to increase the treatment duration for G3 patients to 24 weeks of SOF/RBV [42]. In total, 250 patients with G3 were treated for 24 weeks and 73 patients with G2 were treated for 12 weeks. Treatment-naive G2 patients had strong SVR rates of >97%, matching the results of the POSITRON trial. In G2 treatment-experienced patients the SVR was 91% (30/33) for non-cirrhotic and 88% (7/8) for cirrhotic patients (Figure 1). The disparity for the results for treatment-experienced and cirrhotic patients between the FUSION and VALENCE trial may be attributed to low patient numbers in this subgroup, but other factors may contribute. At the time of writing, the VALENCE trial is not yet pub-

Table 3. Common adverse events (>10%) in Phase III trials with sofosbuvir in hepatitis C virus genotype 2/3.

AE	FISSION		POSITRON		FUSION	
	PEG-IFN/RBV 24 weeks	SOF/RBV 12 weeks	SOF/RBV 12 weeks	Placebo 12 weeks	SOF/RBV 12 weeks	SPF/RBV 16 weeks
Any AE	233 (95.9)	220 (85.9)	185 (89.4)	55 (77.5)	92 (89.3)	86 (87.8)
Anemia	28 (11.5)	20 (7.8)	27 (13)	o	11 (10.7)	4 (4.1)
Neutropenia	30 (12.3)	0	n.a.	n.a.	n.a.	n.a.
Thrombocytopenia	23 (9.5)	0	0	1 (1.4)	2 (1.9)	0
Nausea	70 (28.8)	46 (18.0)	46 (22.2)	28 (39.4)	22 (21.4)	20 (20.4)
Diarrhea	42 (17.3)	23 (9.0)	19 (9.2)	13 (18.3)	15 (14.6)	6 (6.1)
Fatigue	134 (55.1)	92 (35.9)	91 (44)	17 (23.9)	(46 (44.7)	46 (46.9)
Irritability	25 (9.8)	40 (16.5)	19 (9.2)	1 (1.4)	15 (14.6)	11 (11.2)
Headache	102 (44,4)	64 (25)	43 (35.3)	21 (29.6)	(26 (25.2)	32 (32.7)
Insomnia	70 (28.8)	31 (12.1)	39 (18.8)	9 (12.7)	21 (20.4)	28 (28.6)
Pruritus	42 (17.3)	19 (7.4)	23 (11.1)	6 (8.5)	12 (11.7)	7 (7.1)
Arthralgia	35 (14.4)	15 (5.9)	16 (7.7)	1 (1.4)	11 (10.7)	9 (9.2)
Cough	21 (8.6)	19 (7.4)	11 (5.3)	1 (1.45)	10 (9.7)	13 (13.3)
Decreased appetits	44 (18.1)	17 (6.6)	7 (3)	7 (9.9)	9 (8.7)	5 (5.1)
Myalgia	40 (16.5)	21 (8.2)	6 (2.9)	0	8 (7.8)	9 (9.2)
Dizziness	33 (13.6)	27 (10.5)	19 (9.2)	5 (7.0)	6 (5.8)	5 (5.1)
Depression	34 (14)	14 (5.5)	15 (7.2)	1 (1.4)	6 (5.8)	6 (6.1)
RASH	43 (17.3)	23 (9.0)	18 (8.7)	(6 (8.5)	7 (6.8)	12 (12.2)
Influenza like illness	44 (18.1)	7 (2.7)	8 (3.9)	1 (1.4)	1 (1.0)	3 (3.1)
Chills	43 (17.7)	7 (2.7)	7 (3.4)	1 (1.4)	2 (1.9)	0
Pyrexia	33 (13.6)	6 (2.3)	9 (4.3)	0	4 (3.9)	3 (3.1)
Pain	30 (12.3)	5 (2.0)	8 (3.9)	2 (2.8)	4 (3.9)	5 (5.1)
Treatment-related AE						
Grade ≥2 (cirrhosis)	n.a.	14 (28)	7 (22.6)	1 (7.7)	11 (30.6)	11 (34.4)
Grade ≥2 (no cirrhosis)	n.a.	60 (29)	52 (29.5)	11 (19.0)	17 (25.4)	11 (16.7)
SAE (cirrhosis)	n.a.	0	0	0	0	0
SAE (no cirrhosis)	n.a.	1 (0.5)	1 (0.6)	0	0	0

All results are shown as total (%).
AE: Adverse event; n.a.: Not applicable; PEG-IFN: Peg-interferon-α; RBV: Ribavirin; SAE: Serious adverse event; SOF: Sofosbuvir.
Adapted from [38,39].

lished and therefore a thorough comparison between the different trials is not possible.

Treatment prolongation for G3-infected patients showed promising results. For treatment-naive patients the SVR was >92%, regardless of the degree of fibrosis. In treatment-experienced patients without cirrhosis SVR was 87% (87/100) and with cirrhosis 60% (27/45; Figure 1). A further increase in the difficult-to-treat patients with failure of previous treatment and cirrhosis has been demonstrated with the addition of PEG-IFN to SOF/RBV in the LONESTAR-2 trial [43]. 47 patients, who previously failed PEG-IFN/RBV, were treated for 12 weeks. Of these, 26 patients had compensated cirrhosis. 93% with G2 and 83% with G3 achieved SVR. Although this data prove that the addition of PEG-IFN to a SOF/RBV combination is worthwhile in a specific subset of patients, the study population was low in number (Figure 1). Specific interest should be paid to upcoming results in hard-to-treat-subsets of patients. At the time of writing, no complete data regarding baseline characteristics or AEs in the VALENCE-trial or the LONESTAR-2 trial are available.

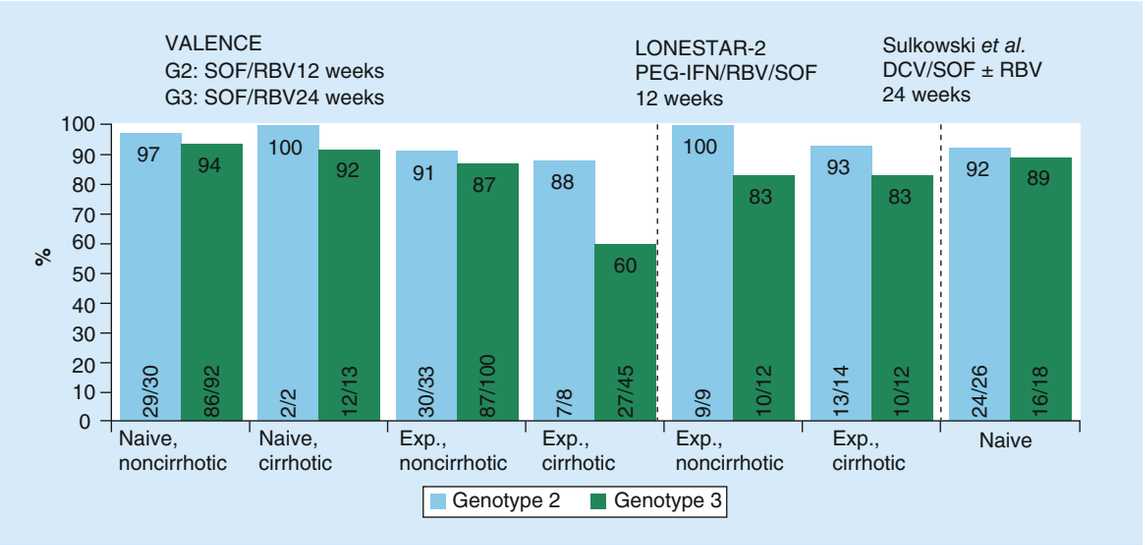

Figure 1 SVR12 results for VALENCE, LONESTAR-2 and the combination of daclatasvir and sofosbuvir.
DCV: Daclatasvir; Exp.: Treatment-experienced; Naive: Treatment-naive; PEG-IFN: Pegylated interferon alpha; RBV: Ribavirin; SOF: Sofosbuvir.
Adapted from [42,43,44].

Another option would be the combination of SOF with another DAA with G3 activity. So far, only data with the combination of SOF plus daclatasvir (DCV), a selective inhibitor of the NS5A replication complex, are available. 18 patients with G3 have been treated with SOF/DCV with or without RBV for 24 weeks and 16 patients achieved SVR (89%; Figure 1) [44]. However, these patients were treatment naive with only few patients with advanced fibrosis.

Conclusion

The development of SOF is clearly a new milestone in the treatment of chronic hepatitis C. The combination of SOF and RBV will be the first interferon-free therapy for patients with G2 and G3. Most of the criticism of current HCV G2 and G3 standard treatment, PEG-IFN and RBV, are perfectly answered with the trials reviewed here. First of all, patients with contraindications to IFN can now be treated. This is of special importance for patients with advanced liver cirrhosis. Second, patients who did not have a treatment option because they failed prior therapy, might now be cured. Third, also rare, but dreaded side effects of interferon treatment like induction of autoimmune disease, severe depression and others are history. Last but not least, many patients did not feel the urge for treatment yet, because they did not notice any hepatitis C-associated symptoms and were scared of the side effects of current interferon-based therapy. Interferon-free schedules may reduce the barrier to treatment. Even in patients who do not respond to SOF/RBV, data hints that due to the high resistance barrier, they may not jeopardize response rates in future treatments.

Still, some open questions remain. Although it is expected that SOF/RBV will become the new SOC with extremely good results in HCV G2 and G3, it may depend on the local health system, who will be eligible for the new therapy. PEG-IFN/RBV may still be a viable option. Especially in patients younger than 50 years of age, PEG-IFN/RBV showed excellent SVR rates and it may be reasonable in treatment-naive patients without contraindications to interferon alfa to start a PEG-IFN based therapy. Although data showed that the expensive triple therapy with BOC or TLV in G1 is cost effective in Spain [45], the UK [46] and USA [47], treatment with SOF/RBV for 12 weeks in G2 and for 24 weeks in G3 adds up to about US$ 80,000–160,000. This may pose a significant challenge even in developed countries. For the same price, several patients could be treated with PEG-IFN/RBV, which may be an attractive alternative for health systems, especially in middle or low income countries. However, the Infectious Diseases Society of America and American Association for the Study of Liver Diseases have recently recommended that SOF/RBV should be the initial therapy in HCV G2 and G3 in patients with or without prior therapy [48].

Another caveat of the Phase II and III trials is the lower response rates in patients with HCV G3, especially those with cirrhosis. In the difficult-to-treat patients with previous treatment failure and cirrhosis even prolongation to 24 weeks of therapy will lead to treatment failures for more than a third of patients.

The poor results of a shorter therapy in cirrhotic patients and the generally poorer response to treatment of HCV G3 in comparison with HCV G2 are in line with previous finding for the PEG-IFN and RBV combination [12,21]. Again, difficult-to-treat patients remain difficult-to-treat patients and a definitive solution is not expected with the approval of SOF. Recommended regimens for SOF for HCV G2- and G3-infected patients as approved by the US FDA are depicted in Box 1. The FISSION, FUSION, POSITRON and VALENCE trial have been considered.

Adding different DAA for combination treatment is the mainstay for interferon-free treatment in G1 right now. SOF and DCV proved to complement each other in G1 treatment, but further development has been cancelled because both drugs are developed by different companies. Although, data for DCV in G2 and G3 is limited, the combination of DCV and SOF might raise SVR rates, especially in G3 patients [44]. In Q3/2014 the approval of DCV is expected and the combination SOF/DCV may be considered for selected difficult-to-treat G3 patients. Several trials with a SOF-based regimens; that is, SOF and ledipasvir, Gilead's own NS5A inhibitor, are being evaluated in G2 and G3; however, trials are ongoing and no results are available at the time of writing [49]. A further option would be the combination of SOF with the cyclophillin inhibitor alisporivir, because alisporivir delivered strong results in HCV G3 [34,35], but so far no data are available.

Hence, given the different options but limited data, the definite medical solution to HCV G3 is still unforeseeable. Most likely a combination treatment of different DAA will increase SVR in hard-to-treat HCV G3 patients and will become the SOC in the future. The challenge will be to identify the best combination and prove the safety and efficacy. For now, PEG-IFN in addition to SOF/RBV might do the trick in patients who are eligible for interferon-based treatment and cannot wait for future options.

Box 1. US FDA label for sofosbuvir in chronic hepatitis C genotype 2 and 3.

- Naive- or treatment-experienced genotype G2: 12 weeks SOF/RBV
- Naive- or treatment-experienced G3: 24 weeks SOF/RBV
- SOF is one 400 mg tablet, taken once daily with or without food
- Dose of RBV is weight-based (<75 kg = 1000 mg and >75 kg = 1200 mg) and taken in two divided doses with food
- Dose reduction and monotherapy with sofosbuvir is not recommended
- No data exit for the dosage of sofosbuvir in patients with severe renal impairment (estimated glomerular filtration rate <30 ml/min/1.73 m^2)

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Executive summary

- Patients with hepatitis C virus (HCV) genotype 3 have a faster progression to cirrhosis than patients with genotype (G) 1 or 2.
- The combination of sofosbuvir (SOF) and ribavirin (RBV) provides a shorter and safer treatment alternative to peg-interferon-α and RBV in HCV G2 and G3.
- SOF and RBV combination is safe and effective in interferon-intolerant patients.
- Patients with G2 show superior response to SOF and RBV compared with G3 patients.
- Patients with HCV G3 and cirrhosis are the most difficult-to-treat patients. Longer treatment duration of 24 weeks SOF/RBV is required.
- Treatment with SOF and RBV in patients with compensated cirrhosis (CHILD A) is safe and treatment-related adverse events were not increased compared with non-cirrhotic patients.
- Patients, who did not respond to prior therapy, have lower sustained virologic response rates than naive patients.
- Treatment prolongation from 12 to 16 or 24 weeks of SOF/RBV does not seem to increase the frequency of side effects.
- Female patients have significantly higher response rates to SOF/RBV treatment than male patients.
- Treatment with SOF and RBV was not associated with viral resistance.
- SOF in combination with peg-interferon-α/RBV or daclatasvir may be considered for selected difficult-to-treat G3 patients.

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