Therapy for Hepatitis C Genotype 3: Moving Forward

M. Buti; J. Llaneras; M. Riveiro-Barciela; R. Esteban

J Viral Hepat. 2015;22(9):683-690.

Abstract and Introduction

Abstract

Until recently, the standard of care for hepatitis C virus genotype 3 infection was response-guided therapy with pegylated interferon plus ribavirin for 16 to 48 or 72 weeks. The introduction of sofosbuvir plus ribavirin has revolutionized hepatitis C virus therapy. Nowadays, the recommend treatment regimen is a combination of sofosbuvir and a weight-based ribavirin dose for 24 weeks. For easy to treat patients (e.g. naïve or previously treated patients without cirrhosis), this combination achieves high sustained virologic response rates and is well tolerated. However, in treatment-experienced patients with cirrhosis, sustained virologic response is lower due to unknown reasons. The combination of two direct-acting antiviral agents, sofosbuvir and daclatasvir, for 12 weeks is also associated with low sustained virologic response rates in this special population, for whom new drugs and different strategies are now under evaluation. Currently, the high cost of all these drugs limits access to treatment in many countries.

Introduction

Several drugs are currently approved for the treatment of chronic hepatitis C genotype 3 (GT3) infection: pegylated interferon alfa 2a or 2b (PegIFN), ribavirin (RBV) and three direct-acting antiviral (DAA) agents, sofosbuvir (SOF), an NS5B polymerase inhibitor; daclatasvir (DCV), an NS5A protease inhibitor; and the combination of SOF plus ledipasvir (LDV), an NS5A protease inhibitor.[1–6] Two therapeutic strategies have been developed using these drugs: (i) interferon-based regimens including PegIFN plus RBV or PegIFN plus SOF and RBV, and (ii) interferon-free regimens, consisting of SOF plus RBV, SOF plus DCV with or without RBV, and SOF plus LDV. Each of these combinations has advantages and disadvantages, as well as differing safety profiles and costs. This article reviews the available therapy and the new treatment agents under development for patients with chronic hepatitis C GT3 infection.

Interferon-based Therapy

At the time of writing, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved two IFN-based therapies for GT3: a combination of PegIFN plus RBV and a combination of PegIFN plus RBV and SOF.

PegInterferon Plus Ribavirin

The PegIFN/RBV combination was the standard of care until approval of the first oral regimen including SOF/RBV.[7,8] The recommended treatment was PegIFN alfa 2a or 2b weekly plus RBV at a fixed dose of 800 mg daily for 24 weeks. The overall sustained virologic response (SVR) rate obtained with this combination was approximately 60% and was higher in noncirrhotic patients (62.7%) than in cirrhotic ones (43%).[9] The most important factor predictive of SVR is achievement of a rapid virologic response (RVR), defined by undetectable hepatitis C virus (HCV) RNA at week 4 of treatment.[9,10] RVR occurred in 60% of GT3 patients and was associated with high SVR rates.[10] In one large study, 86% of GT3 patients who presented RVR subsequently

achieved SVR, *vs* 48–52% of patients who did not present RVR,[11] even when treatment was extended to 48 weeks. In a recent study, including 136 patients with advanced fibrosis treated with 180 μg weekly of PegIFN alfa 2a and 800 mg daily of RBV, SVR rates were 48–42%, regardless of whether therapy was given for 24 or 48 weeks.[12] These data suggest that prolongation of therapy is not appropriate in patients who do not achieve RVR. The main limitation of this regimen is the inclusion of interferon, which makes many patients ineligible for, intolerant to, or unwilling to take the treatment. This combination has a poor safety profile, and many patients require dose reductions or discontinuation due to intolerance. Thus, individuals with mild disease may prefer to wait until new therapy options with better safety profiles become available. Furthermore, patients with cirrhosis, the population most in need of effective treatment, are often ineligible for this combination, show the lowest SVR rates and experience the largest number of adverse events.

There is considerable experience with the PegIFN/RBV combination, as it has been widely used worldwide. Since the emergence of DAA agents, PegIFN/RBV use has dramatically decreased in countries with access to these drugs, but it still remains the only available treatment in some countries, and for this reason, it should be considered a therapeutic option.

Sofosbuvir Plus PegInterferon and Ribavirin

Sofosbuvir is a nucleotide analog inhibitor of the HCV NS5B polymerase, the key enzyme mediating HCV replication. Sofosbuvir is an oral once daily drug that can be administered in combination with pegIFN and RBV or with other DAA agents. The SOF/PegIFN/RBV regimen was initially evaluated in GT3 noncirrhotic naïve patients. The phase II study included 17 patients treated with SOF 400 mg daily plus PegIFN and RBV for either 12 weeks (seven patients) or 8 weeks (10 patients). The overall SVR rate was 100%.[13] In another phase II study (PROTON study), 25 naïve noncirrhotic patients infected by GT2 (N = 15) or GT3 (N =10) received SOF/PegIFN/RBV for 12 weeks. Twenty-three of them (92%) achieved SVR at 12 weeks (SVR12), but there were no data on SVR rates according to genotype.[14] The two patients who were not counted among those achieving SVR did not have treatment failure.

The SOF/PegIFN/RBV combination has also been evaluated in clinical trials including treatment-experienced patients. The associated SVR rates in this population were excellent. This regimen was assessed in a phase II study (LONESTAR 2) in a relatively small number of patients previously treated with pegIFN and RBV.[15] The study included 24 HCV GT3-infected patients, half with liver cirrhosis, who received SOF/PegIFN/RBV for 12 weeks. The overall SVR rate in the series was 83% (20 of 24 patients). Ten of the 12 noncirrhotic patients achieved SVR12, one relapsed and the last was lost to follow-up. Among the 12 cirrhotic patients, 10 reached SVR12, one relapsed, and again, one was lost to follow-up. The adverse events observed were those that typically occur with PegIFN/RBV administration.

Daclatasvir Plus Peginterferon and Ribavirin

Daclatasvir is a selective, first-in-class nonstructural protein 5A (NS5A) replication complex inhibitor with pangenotypic HCV activity and additive to synergistic activity *in vitro* when it is combined with PegIFN or other DAA agents.[5,16] The combination of DCV/PegIFN/RBV showed high SVR rates in patients infected by genotype 1 or 4, with the potential to reduce the duration of treatment from 48 to 24 weeks in most patients.[17] Concerning naïve GT3 patients, a recent phase II study contrasted the efficacy of the DCV/PegIFN/RBV combination during 12 or 16 weeks:[18] In total, 69% and 67% of patients treated for 12 and 16 weeks, respectively, achieved SVR, compared to 59% (16/27) of patients treated with PegIFN/RBV for 24 weeks (). This difference met statistical criteria for noninferiority. The SVR rate was lower in patients with cirrhosis, although the sample included only 11 such cases. The EMA has not approved this combination, likely because of the low SVR rates.

Table 1. SVR in genotype 3 chronic hepatitis C infection treated with approved interferon-based regimens

Treatment	Weeks	Naïve (%)			Treatment-experienced (%)		
		Overall	No Cirrhosis	Cirrhosis	Overall	No Cirrhosis	Cirrhosis
SOF + PegIFN + RBV [13]	8	10/10 (100)	10/10 (100)	–	–	–	–
SOF + PegIFN + RBV [13]	12	7/7 (100)	7/7 (100)	–	–	–	–
SOF + PegIFN + RBV [14]*	12	23/25 (92)	23/25 (92)	–	–	–	–
SOF + PegIFN + RBV [15]†	12	–	–	–	20/24 (83)	10/12 (83)	10/12 (83)
SOF + PegIFN + RBV [22]‡	12	–	–	–	20/22 (92)	NA	NA
DCV + PegIFN + RBV [18]†	12	18/26 (69)	15/19 (79)	3/7 (43)	–	–	–
	16	18/27 (67)	16/23 (70)	2/4 (50)	–	–	–

DCV, daclatasvir; NA, not available; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response. *Patients with genotype 2 and 3 were included. †Patients previously treated with PegIFN and RBV. ‡Patients previously treated with SOF and RBV. §The presence of cirrhosis was not reported in four patients.

Interferon-free Therapies

Currently, there are three IFN-free regimens for GT3 treatment: (i) SOF plus RBV for 24 weeks (approved by the FDA in the USA and EMA in the EU); (ii) DCV plus SOF and RBV for 24 weeks for treatment-experienced patients and those with compensated cirrhosis (approved by both the FDA and EMA); and (iii) SOF plus LDV and RBV for 24 weeks for treating patients with cirrhosis and/or prior treatment failure (only approved by the EMA). The outcomes of these IFN-free regimens are summarized in .

Table 2. SVR in genotype 3 chronic hepatitis C infection treated with interferon-free regimens

Treatment	Weeks	Naïve (%)			Treatment-experienced (%)		
		Overall	No Cirrhosis	Cirrhosis	Overall	No Cirrhosis	Cirrhosis
SOF + RBV [7]	12	102/183 (57)	89/145 (61)	13/38 (34)	–	–	–
SOF + RBV [8]	12	60/98 (61)	57/84 (68)	3/14 (21)	19/64 (30)	14/38 (37)	5/26 (20)
	16	–	–	–	39/63 (62)	25/40 (63)	14/23 (61)
SOF + RBV [19]	24	99/105 (94)	87/92 (96)	12/13 (92)	114/145 (79)	85/98 (87)	29/47 (62)
DCV + SOF +/− RBV [20]	24	16/18 (89)	16/18 (89)	–	–	–	–
DCV + SOF [21]*	12	91/101 (90)	73/75 (97)	11/19	44/51 (86)	32/34 (94)	9/13 (69)

				(58)			
SOF + LDV [23]	12	16/25 (64)	?/22	?/3	–	–	–
SOF + LDV + RBV [23]	12	26/26 (100)	22/22 (100)	4/4 (100)	41/50 (82)	25/28 (89)	16/22 (73)
SOF + GS-5816[†] [27]	8	27/27 (100)	27/27 (100)	–	–	–	–
SOF + GS-5816[†] + RBV [27]	8	21/24 (88)	21/24 (88)	–	–	–	–
SOF + GS-5816[‡] [27]	8	26/27 (96)	26/27 (96)	–	–	–	–
SOF + GS-5816[‡] + RBV [27]	8	26/26 (100)	26/26 (100)	–	–	–	–

DCV, daclatasvir; NA, not available; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response. *For 11 patients, cirrhosis status was missing or inconclusive (FibroTest score >0.48 to <0.75 or APRI >1 to ≤2). [†]GS-5816 at a dose of 25 mg per day; [‡]GS-5816 at a dose of 100 mg per day.

Sofosbuvir and Ribavirin

The first oral IFN-free regimen approved by the FDA in December 2013 for patients infected by GT3 was the combination of SOF plus RBV for 24 weeks. This combination has been evaluated in three phase III studies. The FISSION trial randomized GT2 and GT3 treatment-naïve patients to 12 weeks of SOF/RBV or the standard of care at that time, PegIFN/RBV for 24 weeks.[7] Of the 499 patients enrolled, 20% had compensated cirrhosis and 72% (183 patients) had GT3 infection. Fifty-seven percent (102/183) of GT3 patients treated with SOF/RBV achieved SVR12 compared to 97% of genotype 2 (GT2) patients, a striking difference in response between the two genotypes. Among those treated with PegIFN/RBV for 24 weeks, SVR12 was 63% in GT3 patients and 78% in GT2. This study provided initial evidence of the need for different treatment durations or regimens for each genotype. Noncirrhotic GT2 patients had an SVR rate of 98% compared to 91% of those with cirrhosis. The impact of cirrhosis was much greater in GT3 patients, who showed SVR12 rates of 61% and 34%, respectively.

The phase III POSITRON trial compared SOF/RBV for 12 weeks *vs* placebo in GT2 and GT3 patients who were PegIFN intolerant, ineligible or unwilling.[8] Two hundred and seven patients completed the study, 98 of whom were GT3-infected. The overall SVR12 in patients randomized to treatment with SOF/RBV was 78%. However, once again, there was a significant difference in SVR12 between the two genotypes: 93% for GT2 and 61% for GT3. In GT3 patients with cirrhosis, SVR12 was 21% (3/14) and in noncirrhotic cases, 68% (57/84). As was observed in the FISSION study, cirrhosis was a strong predictor of poor outcome in GT3 patients.

The FUSION trial investigated whether extending the duration of treatment would provide additional benefit in patients failing previous therapy.[8] The study compared 12 to 16 weeks of SOF/RBV in 195 genotype 2 and 3 treatment-experienced patients. Most of them (76%) were relapsers to PegIFN/RBV, and 127 were infected by GT3. SVR12 increased from 86% (31/36) to 94% (30/32) with extended treatment in GT2 patients and from 30% to 62% in GT3 patients. When only cirrhotic patients were evaluated, SVR12 increased from 60% (31/36) to 78% (30/32) with the additional month of treatment in GT2 patients, but the small number of patients included precluded definitive conclusions. In the GT3 cirrhotic group, SVR12 was 20% (5/26) with 12 weeks and 61% (14/23) with 16 weeks of treatment, a striking incremental benefit resulting from four additional weeks of treatment. An increase in the SVR rate was also observed in patients without cirrhosis (37% vs 63%).

The VALENCE trial evaluated 24 weeks of SOF/RBV in 250 treatment-naïve and treatment-experienced patients with GT3, including approximately 24% of patients with liver cirrhosis.[19] In treatment-naïve patients, 96% of those without cirrhosis achieved SVR12 compared to 92% with cirrhosis. However, in treatment-experienced patients who did not respond to PegIFN/RBV therapy, SVR12 was 87% in the noncirrhotic population and 62% in cirrhotic patients. Another important finding from this study was that SVR rates were not influenced by RBV dose reduction or interruption. In fact, SVR was 100% in the 13 patients who required RBV dose modification and 85% in the 235 patients who did not. Early viral response, defined by an undetectable viral load at weeks 2 and 4, was similar between treatment-naïve and treatment-experienced patients and also between patients with and without cirrhosis. On multivariate logistic regression analysis, the factors associated with SVR12 were age (<50 *vs* ≥50 years) with an odds ratio (OR) of 2.8, female *vs* male sex (OR 3.180), presence of liver cirrhosis (OR 3.46), and baseline HCV RNA below or above 10^6 IU/mL (OR 4.2). Therapy was well tolerated, and the most common adverse effects were headache, fatigue and pruritus. The S282T variant was the only mutation related to reduced susceptibility to SOF *in vitro*. This variant was not detected in any of the 41 patients who presented virologic failure to SOF, even by deep sequencing. Therefore, up to now, SOF resistance has not been described in GT3-infected patients treated with SOF/RBV.

Based on the results of the VALENCE study, the current recommendation for SOF/RBV in GT3 patients is 24 weeks of treatment regardless of the presence of cirrhosis.[1]

Sofosbuvir and Daclatasvir

The efficacy and safety of DCV 60 mg once a day in combination with SOF 400 mg daily for 24 weeks, with or without RBV, were evaluated in an open-label randomized study (AI444040),[20] including 18 patients. Based on FibroTest findings, 30% of patients presented ≥F3 liver fibrosis, but no cirrhosis. SVR12 was achieved by 89% of patients: 85% treated with SOF/DCV for 24 weeks and 100% treated with SOF/DCV/RBV for 24 weeks. Only five patients had >F3 fibrosis and all five achieved SVR12. The therapy was well tolerated, and no new side effects were reported. DCV has been approved only in Europe. DCV is currently recommended in combination with SOF and RBV for 24 weeks in GT3 patients who are treatment-experienced and/or have compensated cirrhosis.[1]

The combination of SOF plus DCV without RBV for both naïve and treatment-experienced patients was evaluated in the ALLY-3 study.[21] One hundred and fifty-two patients were included, 101 treatment-naive and 51 treatment-experienced. Those patients had previously failed treatment with interferon-based therapies or other anti-HCV therapies, including SOF (n = 7) and alisporivir (n = 2). Nineteen (19%) naïve patients and 13 (25%) previously treated patients presented liver cirrhosis, determined by liver biopsy, FibroScan (>14.6 kPa), FibroTest (score >075) or APRI (score >2). All received DCV 60 mg plus SOF 400 mg daily for 12 weeks. SVR12 rates were 90% in treatment-naïve and 86% in treatment-experienced patients. All patients, except one, achieved end of treatment response. In treatment-naive patients, SVR was 97% in patients without cirrhosis and 58% in those with cirrhosis. Regarding treatment-experienced cases, SVR was 94% and 69% in patients without and with cirrhosis. Sixteen patients relapsed; nine were naïve and seven treatment-experienced. Eleven of the 16 patients who relapsed presented liver cirrhosis. Resistance-associated variants (RAVs) related to NS5A resistance were detected in 9 of the 16 patients who relapsed. The most common adverse events reported were headache, fatigue and nausea in 12% of patients. The SOF/DCV combination yields very high SVR rates in noncirrhotic patients (96%), but in those with cirrhosis, the overall SVR of 63% is disappointing.

In summary, for patients with cirrhosis, the SOF/DCV combination during 12 weeks is suboptimal. Further options for optimizing treatment outcomes with SOF/DCV, such as addition of RBV or extending treatment to 16 weeks, are now under evaluation.

Sofosbuvir Plus PegInterferon and Ribavirin After Sofosbuvir Plus Ribavirin Failure

The efficacy of SOF-containing regimens in patients who failed to achieve SVR with SOF is unknown. Given the lack of genotypic or phenotypic resistance to SOF in patients who did not achieve SVR in the phase III programme, an open-label study was designed for relapsers, in which patients would receive either SOF/RBV for a longer time or SOF/PegIFN/RBV.[22] HCV-infected GT2 and GT3 patients who failed 12- or 16-week regimens of SOF/RBV (phase III studies: FISSION, FUSION, and POSITRON) were offered either 12 weeks of SOF (400 mg once daily) plus PegIFN (180 mg weekly) and RBV (1000–1200 mg daily) or an interferon-free 24-week arm of SOF/RBV. The choice of regimen was at the discretion of the investigator. A total of 97 GT3 and 16 GT2 patients were enrolled. Most patients were male (80%) and had a non-IL28CC genotype (65%); 33% of patients had cirrhosis. To date, 50 patients have been analysed: 22 received SOF/PegIFN/RBV and 38 were re-treated with SOF/RBV for 24 weeks; 34% and 41% had cirrhosis, respectively. The preliminary results showed an SVR rate of 92% (20/22) in patients receiving SOF/PegIFN/RBV and 63% (24 of 38) in those receiving SOF/RBV for 24 weeks. There is still no data regarding the influence of cirrhosis on SVR in GT3 patients. The safety profile was better for the SOF/RBV combination. Although the study includes only a small number of patients with cirrhosis, this factor did not seem to have an impact on response in patients treated with SOF/PegIFN/RBV.

Re-treatment with this regimen is also an attractive option from the economic viewpoint because of the short duration of the therapy (12 weeks) for HCV GT3-infected patients who fail to achieve SVR with SOF/RBV.

Sofosbuvir Plus Ledipasvir With or Without Ribavirin

Ledipasvir (LDV) is a potent inhibitor of HCV NS5A, a viral phosphoprotein that plays an important role in viral replication, assembly and secretion. LDV has shown additive to moderately synergistic antiviral activity when used with other DAA agents against HCV.

The ELECTRON-2 trial explored the efficacy and safety of SOF plus LDV in 51 treatment-naïve patients with GT3 infection.[23] Patients were randomized equally to receive a fixed-dose combination of SOF 400 mg plus LDV 90 mg daily with or without RBV for 12 weeks. SVR12 rates were 64% for the regimen without RBV and 100% with RBV. The latter group included only four patients with liver cirrhosis, and all achieved SVR12. The treatment was well tolerated. Consistent with the safety profile of RBV, adverse events and laboratory abnormalities were more common in the RBV-containing group. This combination has the potential to cure more than half of patients treated with the two oral DAAs and all patients with addition of RBV. The number of cases is relatively small, but the response rate improved with the addition of RBV.

The SOF/LDV/RBV combination has also been examined in treatment-experienced patients with and without cirrhosis. Fifty HCV GT3 patients, 22 of them with liver cirrhosis, were treated with this combination for 12 weeks.[23] The overall SVR12 was 82%, that is, 89% (25/28) in patients without cirrhosis and 73% (16/22) in those with cirrhosis. No new side effects were reported. Deep-sequencing analysis of NS5A and NS5B was performed in six of the nine patients who did not achieve SVR12. No NS5A resistance-associated variants were detected in five of the six patients, and a low level of the Y93C variant was found in one patient. None of the patients developed NS5B mutations.

The combination of LDV/SOF for 24 weeks has been approved by EMA in Europe for patients with compensated cirrhosis or prior treatment failure.[6,24] However, efficacy is higher when RBV is added to this regimen.[23]

Current Scenario

In most countries, oral therapy is prioritized for patients with advanced fibrosis (F3 and F4). Patients with a lower degree of liver fibrosis are still treated with PegIFN-based regimens or are waiting for broader indications for DAA agents. The combination of SOF/RBV has several advantages. It is simple, orally administered, has

high applicability and yields excellent SVR rates in naïve patients, including those with cirrhosis. However, this regimen is suboptimal for previously treated patients with cirrhosis (SVR rates of 60%),[7,8] and 24 weeks of treatment are required, with the subsequent cost increase.[19] The same occurred when 2 DAA agents were combined:[20,21,23] SVR rates were excellent in patients without liver cirrhosis, but much lower when cirrhosis was present. For both combinations, SOF/DCV and SOF/LDV, RBV addition increased the SVR rates in cirrhotic patients. The SOF/PegIFN/RBV regimen has many advantages: high SVR rates (>90% even in patients with cirrhosis), shorter therapy duration and capability to cure patients who relapsed after treatment with SOF/RBV.[13,15] It is less expensive than 24 weeks of SOF/RBV or two DAA agents. However, it presents all the limitations of IFN-containing regimens: low applicability, many unwilling patients, and adverse effects; in addition, use of an IFN-based therapy requires a more experienced physician. To date, there are no cost-effectiveness studies comparing these two regimens. However, there is an ongoing phase III trial named BOSON, a multicenter study that has enrolled 592 naïve and treatment-experienced HCV GT2 and GT3 patients with or without cirrhosis.[25] Patients have been randomized to receive SOF/RBV for 16 weeks, SOF/RBV for 24 weeks or SOF/PegIFN/RBV for 12 weeks. The preliminary results from this study, recently reported in the annual European Association for the Study of the Liver (EASL) meeting, showed higher SVR rate in patients treated with SOF/PegIFN/RBV (168/181, 93%) in contrast with those patients treated with SOF/RBV for 16 weeks (128/181, 71%) or 24 weeks (153/182, 84%), even for previously treated cirrhotics patients (47% vs 77% vs 86%, for SOF/RBV during 16 weeks, 24 weeks or SOF/PegIFN/RBV for 12 weeks, respectively). Based on the current results, a proposal of therapy regimens for treatment of GT3 infection is summarized in .

Table 3. Proposal of therapy regimens for treatment of hepatitis C virus genotype 3 according to the degree of fibrosis

	No Cirrhosis	**Cirrhosis**
Naïve	SOF + RBV for 24 weeks SOF + DCV for 12 weeks	SOF + RBV for 24 weeks
Treatment experienced	SOF + RBV for 24 weeks SOF + DCV for 12 weeks	SOF + pegIFN + RBV for 12 weeks SOF + DCV + RBV for 24 weeks

DCV, daclatasvir; LDV, ledipasvir; PegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir.

Drugs Under Development for Genotype 3

Various pharmaceutical companies are now conducting several studies including new drugs, particularly NS5A inhibitors ().

Table 4. Direct-acting agents and host-targeting antivirals with activity against hepatitis C virus genotype 3

			NS5B		
	NS3/NS4A protease inhibitors	**NS5A inhibitors**	**Nucleos(t)ide analogs**	**Non-nucleoside analogs**	**Cyclophilin A inhibitors**
Drugs approved		Daclatasvir Ledipasvir	Sofosbuvir		
Drugs under evaluation	Grazoprevir ACH-2684	Elbasvir Ombitasvir ACH-3102	Mericitabine VX-135 VX-222	Dasabuvir BMS-791325 TMC647055	Alisporivir SCY-635

		GS-5816 IDX-719		Setrobuvir	

Sofosbuvir and GS-5816

GS-5816 is an HCV NS5A inhibitor with potent activity against HCV genotypes 1 to 6, as has been demonstrated in a 3-day monotherapy study.[26] In the ELECTRON-2 study, naïve noncirrhotic GT3-infected patients were randomized to receive SOF 400 mg once a day plus 2 different doses of GS-5816 with or without RBV during 8 weeks: GS-5816 25 mg once daily plus SOF with or without RBV or GS-5816 100 mg once daily plus SOF with or without RBV. One hundred and four patients were included in this 4-arm phase II study.[27] SVR rates were 88% and 100% for patients treated with 25 mg of GS-5816 with or without RBV, and 96% and 100% for those treated with 100 mg of GS-5816 with or without RBV, respectively. Only two patients relapsed. The most common adverse events (>10%) were fatigue, headache and nausea and were related to RBV.

Alisporivir Monotherapy or in Combination With Ribavirin or PegInterferon Plus Ribavirin

Alisporivir (ALV) is a host-targeting antiviral with pangenotypic anti-HCV activity and a high barrier to viral resistance. ALV has been analysed in the VITAL-1 study, a multicenter trial that included HCV GT2 and GT3 infected patients.[28] In total, 340 treatment-naïve HCV GT2 or GT3 patients were randomized to five arms: (i) ALV 1000 mg daily in monotherapy (n = 83), (ii) ALV 600 mg daily plus RBV (n = 84), (iii) ALV 800 mg daily plus RBV (n = 94), (iv) ALV 600 mg daily plus PegIFN (n = 39) and (v) PegIFN plus RBV (n = 40). Patients in the ALV-containing arms with detectable viral load at week 4 continued treatment with ALV/PegIFN/RBV triple therapy from week 6 to 24. In the IFN-free treatments, SVR rates were 91–93% in the ALV/RBV arms and 82% in patients receiving ALV monotherapy. Of 177 patients receiving IFN-free regimens with ALV/RBV from baseline and ALV/RBV interferon add-on, 90% presented SVR12, *vs* 88% and 72% with standard PegIFN/RBV, respectively. There were no differences in response to ALV treatment between GT2 and GT3 patients. ALV treatments were well tolerated. Discontinuation rates were lower, and there were markedly fewer flu-like symptoms compared with PegIFN/RBV. Transient hyperbilirubinemia (>5 × ULN) with ALT normalization occurred in six (2%) patients treated with ALV.

Novartis has discontinued development of alisporivir due to pancreatitis cases occurring when this drug was given with PegIFN in GT1 patients.

Other Combinations

Abbvie has evaluated the efficacy of a NS3/4 inhibitor, ABT450/r, combined with ABT267 (NS5A inhibitor) with or without RBV for 12 weeks in a small number of treatment-naïve noncirrhotic HCV GT3 patients. SVR was documented in 4 of 10 (40%) patients treated with ABT450/r/ABT267 and in 1 of 11 (9%) treated with ABT450/r/ABT267/RBV.[29]

In addition, there is an ongoing open-label pilot study to evaluate the efficacy and safety of a more potent NS5A inhibitor, ABT 530 in combination with ABT-450/r with or without RBV during 12 weeks for naïve GT3 patients with cirrhosis. The results of this study are expected by 2015.

Merck has an ongoing study for GT3 patients using a regimen that includes three oral antivirals, a potent NS3 inhibitor (MK-5172), an NS5A inhibitor (MK-8742 or MK-8408) and a non-nucleoside inhibitor (MK-3682) during 12 weeks. The study is currently recruiting patients.[30]

Summary

In summary, therapy for patients infected by HCV GT3 is moving forward. Sofosbuvir has represented a major advance in the treatment of GT3 patients. In treatment-naïve patients with or without cirrhosis, the combination of SOF/RBV for 24 weeks achieves high SVR rates. However, in treatment-experienced patients with cirrhosis, SOF/RBV for 24 weeks or two direct antivirals such as SOF/DCV for 12 weeks offer lower 'cure' rates (SVR12 of approximately 60%). For these patients, new drugs are now under investigation with promising preliminary results. In the meantime, the combination of SOF/PegIFN/RBV for 12 weeks is the best available option. The main drawback to the interferon-free regimens is the high cost of the drugs, an important constraint in countries with limited resources.

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2014; 60(2): 392–420.
2. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; 49(4): 1335–1374.
3. AASLD. Recommendations for Testing, Managing, and Treating Hepatitis C. AASLD, 2014. http://www.hcvguidelines.org (accessed 5 February 2015)
4. Sovaldi: EPAR- product information. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002798/human_med_001723.jsp&mid=WC0b01ac058001d124 (accessed 2 February 2015).
5. Daklinza: EPAR: product information. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003768/human_med_001792.jsp&-mid=WC0b01ac058001d124 (accessed 3 February 2015).
6. Harvoni: EPAR- product information. 2014. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003850/human_med_001813.jsp&mid=WC0b01ac058001d124 (accessed 3 February 2015).
7. Lawitz E, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; 369(7): 678–679.
8. Jacobson IM, Gordon SC, Kowdley KV *et al.* Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; 368(20): 1867–1877.
9. Marcellin P, Cheinquer H, Curescu M *et al.* High sustained virologic response rates in rapid virologic response patients in the large real-world PROPHESYS cohort confirm results from randomized clinical trials. *Hepatology* 2012; 56(6): 2039–2050.
10. Fried MW, Hadziyannis SJ, Shiffman ML, Messinger D, Zeuzem S. Rapid virological response is the most important predictor of sustained virological response across genotypes in patients with chronic hepatitis C virus infection. *J Hepatol* 2011; 55(1): 69–75.
11. Di Martino V, Richou C, Cervoni JP *et al.* Response-guided peg-interferon plus ribavirin treatment duration in chronic hepatitis C: meta-analyses of randomized, controlled trials and implications for the future. *Hepatology* 2011; 54(3): 789–800.
12. Shoeb D, Dearden J, Weatherall A *et al.* Extended duration therapy with pegylated interferon and ribavirin for patients with genotype 3 hepatitis C and advanced fibrosis: final results from the STEPS trial. *J Hepatol* 2014; 60(4): 699–705.
13. Gane EJ, Stedman CA, Hyland RH *et al.* Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013; 368(1): 34–44.
14. 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(5): 401–408.
15. Lawitz E, Poordad F, Brainard DM *et al.* Sofosbuvir with peginterferonribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. *Hepatology* 2015; 61(3): 769–775.

16. Pelosi LA, Voss S, Liu M, Gao M, Lemm JA. Effect on hepatitis C virus replication of combinations of direct-acting antivirals, including NS5A inhibitor daclatasvir. *Antimic-rob Agents Chemother* 2012; 56(10): 5230–5239.
17. Hezode C, Hirschfield GM, Ghesquiere W *et al.* Daclatasvir plus peginterferon alfa and ribavirin for treatment-naive chronic hepatitis C genotype 1 or 4 infection: a randomised study. *Gut* 2014; doi: 10.1136/gutjnl-2014-307498. [Epub ahead of print]
18. Dore GJ, Lawitz E, Hezode C *et al.* Daclatasvir plus peginterferon and ribavirin is noninferior to peginterferon and ribavirin alone, and reduces the duration of treatment for HCV genotype 2 or 3 infection. *Gastroenterology* 2015; 148(2): 355–366 e1.
19. Zeuzem S, Dusheiko GM, Salupere R *et al.* Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; 370(21): 1993–2001.
20. 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(3): 211–221.
21. 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 3 study. *Hepatology* 2015; 61(4): 1127–1135.
22. Esteban R, Lalezari J, Ni L *et al.* Successful Retreatment with Sofosbuvir-containing regimens for HCV genotype 2 or 3 infected patients who failed prior sofosbuvir plus ribavirin therapy. *J Hepatol* 2014; 60(1): S4–S5.
23. Gane EJHR, An D, Pang PS, Symonds WT, Mchutchison JG, Stedman CA. Sofosbuvir/Ledipasvir fixed dose combination is safe and effective in difficult-to-treat populations including genotype-3 patients, decompensated genotype-1 patients and genotype-1 patients with prior sofosbuvir treatment experience. *J Hepat* 2014; 60: S3–S4.
24. Harvoni recommended for the treatment of chronic hepatitis C. Avail able at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/09/news_detail_002175.jsp&mid=WC0b01ac058004d5c1 (accessed 4 May 2015).
25. Foster GR, Pianko S, Cooper C, Brown A, Forton D, Nahass RG, George J, Barnes E, Brainard DM, Massetto B, Lin M, McHutchison JG, Subramanian GM, Agarwal K. Sofosbuvir + PegInterferon/Ribavirin for 12 weeks vs Sofosbuvir + Ribavirin for 16 or 24 weeks in Genotype 3 HCV infected patients and treatment-experienced cirrhotic pacientes with genotype 2 HCV: The BOSON study. *J Hepatol.* 2015; 62: S259–S260.
26. Cheng GYM, Peng B, Lee YJ *et al.* GS-5816, a second generation HCV NS5A inhibitor with potent antiviral activity, broad genotypic coverage and a high resistance barrier. *J Hepatol* 2013; 58: S484–S485.
27. Gane EJHR, An D, McNally J *et al.* Once daily sofosbuvir with GS-5816 for 8 weeks with or without ribavirin in patients with HCV genotype 3 without cirrhosis result in high rates of SVR12: the ELECTRON2 study. *Hepatology* 2014; 60(S1): 236A–237A.
28. Pawlotsky JMSS, Foster G, Peng CY, Rasenack J, Flisiak R. Alisporivir plus ribavirin is highly effective interferon-free or interferon-add-on regimen in previously untreated HCV-GT2 or GT3 patients: SVR12 results from VITAL-1 phase 2B study. *J Hepatol* 2012; 56(2): S553.
29. Lawitz E, Sullivan G, Rodriguez-Torres M *et al.* Exploratory trial of ombitasvir and ABT-450/r with or without ribavirin for HCV genotype 1, 2, and 3 infection. *J Infect* 2015; 70(2): 197–205.
30. Efficacy and Safety of Grazoprevir (MK-5172) and MK-3682 With Elbasvir (MK-8742) or MK-8408 for Chronic Hepatitis C Infection (MK-3682-011). Available at: https://clinicaltrials.gov/ct2/show/NCT02332707 (accessed 3 February 2015).

Abbreviations

ALV, Alisporivir; DAA, direct-acting antiviral; DCV, daclatasvir; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCV, hepatitis C virus; LDV, ledipasvir; OR, odds ratio; PegIFN, pegylated interferon; RBV, ribavirin; RVR, rapid virologic response; SOF, sofosbuvir; SVR, sustained virologic response.

Acknowledgements
Writing support was provided by Celine Cavallo.

J Viral Hepat. 2015;22(9):683-690.