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THE LIVER MEETING 2014:

Summary of presentations from the 65th Annual Liver Meeting of the American Association for the Study of Liver Diseases (AASLD), held in Boston, Massachusetts, USA, on 7th-11th November 2014

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ABSTRACT

Rapid developments in clinical research on the hepatitis C virus infection in the last few years have led to the development of direct-acting antivirals, such as sofosbuvir, simeprevir (both of which have been approved in the US and Europe since 2014), and daclatasvir, which was approved in Europe only in 2014. These new drugs generated a change of paradigm from interferon-based therapies, as the former require shorter treatment durations and provide high cure rates with acceptable toxicity. The 65th American Association for the Study of Liver Diseases (AASLD) Annual Meeting, The Liver Meeting® 2014, took place in Boston, Massachusetts, on 7th-11th November. This review will summarise the highlights of this meeting within the context of pivotal clinical trials and real-life data on this rapidly evolving treatment environment, which will assist clinicians in selecting the most appropriate regimen for patients.

Keywords: Hepatitis C virus infection, direct-acting antivirals, sofosbuvir, daclatasvir, ledipasvir, GS-5816, simeprevir.

INTRODUCTION

Rapid developments in clinical research on the hepatitis C virus (HCV) infection in the last few years have led to the development of direct-acting antivirals (DAAs), such as sofosbuvir (SOF), a pangenotypic polymerase (NS5B) inhibitor, and simeprevir (SMV), a potent NS3-4A protease inhibitor, both of which were approved in the US and Europe in 2014, and daclatasvir (DCV), a potent, pangenotypic NS5A inhibitor,[1] which was approved in Europe only in 2014. These new drugs generated a change of paradigm from interferon (IFN)-based therapies, as the former require shorter treatment durations and provide high cure rates with acceptable toxicity. The 65th American Association for the Study of Liver Diseases (AASLD) Annual Meeting, The Liver Meeting® 2014, took place in Boston, Massachusetts, on 7th-11th November. This review will summarise the highlights of this meeting within the context of pivotal clinical trials and real-life data on this rapidly evolving treatment environment, focusing on oral therapy for hepatitis C (Table 1).

Table 1: Key clinical data presented at the American Association for the Study of Liver Diseases 2014.

GT	Patient characteristics	Previous therapy	Subpopulation	Study name, reference	Type of study	Investigated compounds	Treatment duration	n
1-6	Non-cirrhotic patients	TN		[27,28]	Phase II open-label study	SOF + GS-5816±RBV	8 or 12 weeks	154
1		TN		UNITY-1[33]	Multicentre, nonrandomised, open-label Phase III trial	DCV+ASV+BCV	12 weeks	415
3		TN		ELECTRON-2[30]	Phase II open-label study	SOF + GS-5816±RBV	8 weeks	104
1	Cirrhotic or non-cirrhotic patients	TN	Non-cirrhotic	C-SWIFT[41]	Open-label phase II trial	GZV+EBV+SOF	4 or 6 weeks	102
			Cirrhotic				6 or 8 weeks	
1		TE	Failure to SOF	[18]	Single-arm Phase II study	SOF+LDV+RBV	12 weeks	51
1		TN/TE		C-WORTHY[42]	Open-label Phase II	GZV+EBV+SOF +/-RBV	12-18 weeks	253
1a		TN or TE		[35]	Pooled analysis from Phase III clinical trials	PRV+RTV+OBV +DBV+/-RBV	12 or 24 weeks	1,058
1/3		TN		[5]	Prospective randomised national study	SOF + RBV	16 or 24 weeks	127
1-3*		PI-failures	Non-cirrhotic or cirrhotics GT1	[29]	Phase II study	SOF + GS-5816±RBV	12 weeks	321
		TE	Non-cirrhotic GT3					
			Cirrhotic GT3					
1-3		TN or TE		HCV-TARGET[14]	Longitudinal observational cohort study	SOF-containing regimens	N/A	2,063
1-4		TN or TE	Post-transplant patients	HCV-TARGET[15]	Longitudinal observational cohort study	SOF-containing regimens	N/A	227
		TN	GT1 HIV co-infected	PHOTON 1 & 2[7]	Phase III study	SOF + RBV	24 weeks	497
			GT2 HIV co-infected				12 weeks	
		TE					24 weeks	
		TN	GT3 HIV co-infected				12 weeks	
							24 weeks	
		TE					24 weeks	
		TN	GT4 HIV co-infected				24 weeks	
3		TN	GT3	ALLY-3[12]	Phase III study	SOF + DCV	12 weeks	152
		TE				SOF + DCV	12 weeks	
3/6		TE	GT3	[17]	Phase II multicentre, open-label study	SOF+LDV+RBV	12 weeks	75
		TN/TE	GT6			SOF + LDV	12 weeks	
1	Cirrhotic patients	DAA-naïve		TURQUOISE-II[38]	Open-label, prospective, randomised Phase III trial	PRV+RTV+OBV +DBV+RBV	12 vs 24 weeks	380
1		TN or TE	Compensated cirrhosis	[16]	Pooled analysis from Phase II/III clinical trials	LDV/SOF regimens	12 or 24 weeks	513

Table 1 continued.

GT	Patient characteristics	Previous therapy	Subpopulation	Study name, reference	Type of study	Investigated compounds	Treatment duration	n
1/4	Cirrhotic patients	TN or TE	Decompensated cirrhosis	SOLAR-1[20]	Prospective, randomised, multicentre study	LDV/SOF+RBV	12 or 24 weeks	108
1		TN TE		UNITY-2[34]	Multicentre, randomised, double-blind Phase III trial	DCV+ASV+BCV	12 weeks	202
1		PI-failures	Compensated cirrhosis	SIRIUS[19]	Multicentre, randomised, double blind Phase II trial	LDV/SOF+RBV	12 weeks	154
1						LDV/SOF	24 weeks	

*Data on GT3 patients not presented.
ASV: asunaprevir; BCV: beclabuvir; DAA: direct-acting antiviral; DBV: dasabuvir; DCV: daclatasvir; EBV: Epstein-barr virus; GT: genotype; GZV: grazoprevir; HCV: hepatitis C virus; LDV: ledipasvir; OBV: ombitasvir; pegIFN: pegylated-interferon; PI: protease inhibitors; PRV: paritaprevir; RBV: ribavirin; RTV: ritonavir; SMV: simeprevir; SOF: sofosbuvir; SVR4: sustained virologic response at week 4; SVR4/8: sustained virologic response at either 4 or 8 weeks after completing therapy; SVR12: sustained virologic response 12 weeks after completion of therapy; TE: treatment-experienced; TN: treatment-naïve.

SOFOSBUVIR-BASED REGIMENS

Sofosbuvir + Ribavirin

SOF is a once-daily pangenotypic nucleotide NS5B polymerase inhibitor with demonstrated potent activity against GT1-6 and a good safety profile.[2-4]

Common patient populations

Genotype 3

Cirrhotic and non-cirrhotic/treatment-naïve patients

An IFN-free regimen of SOF+ribavirin (RBV; 16 or 24 weeks) was evaluated across 16 Russian centres encompassing 127 treatment-naïve patients, of which 66 were genotype 1 (GT1) and 61 were GT3; 17% of them had compensated cirrhosis.[5] After 16 weeks of therapy, sustained virologic response at post-treatment week 12 (SVR12) rates in the GT1 and GT3 cohorts were 50% (Tables 2-4) and 87% (Table 6) while after 24 weeks they reached 76% and 90%, respectively, demonstrating high rates for the 16-week arm in GT3 patients, which were very close to that observed in the 24-week arm. Of note, current AASLD guidelines recommend SOF+RBV for 24 weeks in this subpopulation (Class I, Level B recommendation).[6] However, in GT1 patients, the SOF+RBV combination for 16 or 24 weeks was suboptimal in this patient population. Overall, the safety profile for this combination was consistent with that of RBV monotherapy; the combination was well tolerated with no patients discontinuing treatment due to adverse events (AEs).

Specific patient populations

Genotypes 1-4

HIV co-infection: PHOTON-1 and PHOTON-2

The PHOTON-1 and 2 Phase III studies[7] were conducted to evaluate the efficacy and safety (as well as co-administration with antiretrovirals) of once-daily SOF+RBV for 12 or 24 weeks in 497 GT1-4 patients with concurrent HIV infection. GT1 treatment-naïve patients (n=226) received SOF+RBV for 24 weeks; GT2 treatment-naïve patients (n=45) received the regimen for 12 weeks, while treatment-experienced patients (n=30) were treated for 24 weeks. GT3 patients were assigned to one of three groups: treatment-naïve patients receiving combination therapy for 12 weeks (n=42), treatment-naïve patients receiving treatment for 24 weeks (n=57), or treatment-experienced patients also treated for 24 weeks (n=66). GT4 treatment-naïve patients (n=31) received SOF+RBV for 24 weeks.

SVR12 rates were high in all subgroups (≥81%, Tables 2-7) and comparable with results in monoinfected

patients, except for treatment-naïve GT3 patients in the 12-week treatment subgroup (67%), thus supporting the superiority of the 24-week modality as previously established in the VALENCE study.[8] Cirrhosis presence did not seem to have an impact on SVR12 rates in GT2-4 patients. Overall, the regimen was well tolerated and there was no change in CD4 T-cell percentage during treatment.

Table 2: Key results from studies presented at the American Association for the Study of Liver Diseases 2014: GT1 patients, overall population.

Study	Treatment arms/subgroups	Duration (weeks)	n	TN/TE	Subgroup 1	Subgroup 2	SVR12 (%) or primary endpoint
GENOTYPE 1							
OVERALL POPULATION							
Prospective randomised national study[5]	SOF+RBV	16	32	TN			50
		24	34				76
PHOTON 1 & 2[7]	SOF+RBV	24	226	TN	HIV co-infection		81
Phase II study[29]	SOF+GS-5816 25 mg	12	27	TE	PI-failures		100
	SOF+GS-5816 25 mg +RBV		29				97
	SOF+GS-5816 100 mg		27				100
	SOF+GS-5816 100 mg +RBV		28				96
HCV-TARGET[14]	SOF+SMV+/-RBV	N/A	303	TN/TE			SVR4 89
	SOF+RBV+pegIFN		164				SVR4 85
HCV-TARGET subanalysis[15]	SOF+SMV+/-RBV	N/A	68	TE	Post-transplant		SVR4 90
	SOF+RBV+pegINF		12				SVR4 83
Single-arm Phase II study[18]	LDV+SOF+RBV	12	50	TE	SOF-failures		100
UNITY-1[33]	DCV+ASV+BCV	12	415	TN/TE			91
C-WORTHY[42]	GZV+EBV	12	33	TE	Previous null response to pegINF/RBV		91
	GZV+EBV+RBV		32				94
	GZV+EBV	18	32				97
	GZV+EBV+RBV		33				100

SVR12/primary endpoint coding: dark green: 100%; green: 90-99%; yellow: 80-89%; orange: 70-79%; red: <70%.
ASV: asunaprevir; BCV: beclabuvir; DCV: daclatasvir; EBV: epstein-barr virus; GZV: grazoprevir; LDV: ledipasvir; N/A: not applicable; pegIFN: pegylated-interferon; PI: protease inhibitors; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; SVR4: sustained virologic response at week 4; SVR12: sustained virologic response 12 weeks after completion of therapy; TE: treatment-experienced; TN: treatment-naïve.

Table 3: Key results from studies presented at the American Association for the Study of Liver Disease 2014: GT1 non-cirrhotic patients.

Study	Treatment arms/subgroups	Duration (weeks)	n	TN/TE	Subgroup 1	Subgroup 2	SVR12 (%) or primary endpoint
GENOTYPE 1							
NON-CIRRHOTIC							
Prospective randomised national study[5]	SOF+RBV	16	28	TN			57
		24	28				86

Table 3 continued.

Study	Treatment arms/subgroups	Duration (weeks)	n	TN/TE	Subgroup 1	Subgroup 2	SVR12 (%) or primary endpoint
PHOTON 1 & 2[7]	SOF+RBV	24	204	TN	HIV co-infection		82
SOF+GS-5816 Part A[27,18]	SOF+GS-5816 25 mg	12	27	TN			96
	SOF+GS-5816 100 mg		28				100
SOF+GS-5816 Part B[27]	SOF+GS-5816 25 mg	8	30	TN			87
	SOF+GS-5816 25 mg +RBV		30				83
	SOF+GS-5816 100 mg		29				90
	SOF+GS-5816 100 mg +RBV		31				81
HCV-TARGET[14]	SOF+SMV+/-RBV	N/A	123	TN/TE			SVR4 92
	SOF+RBV+pegIFN		127				SVR4 90
HCV-TARGET subanalysis[15]	SOF+SMV+/-RBV	N/A	31	TE	Post-transplant		SVR4 94
UNITY-1[33]	DCV+ASV+BCV	12	312	TN	Overall		92
			229		HCV subtype	GT1a	90
			83			GT1b	98
			103	TE	Overall		89
			75		HCV subtype	GT1a	85
			28			GT1b	100
Pooled analysis from SAPPHIRE-I, SAPPHIRE-II, TURQUOISE-II and PEARL-IV (GT1a)[35]	PRV+RTV+OBV+DBV	12	202	TN			90
	PRV+RTV+OBV+DBV+RBV		593	TN/TE			96
			420	TN			96
			50	TE	Relapse		94
			36		Partial response		100
			87		Null response		95
C-SWIFT[41]	GZV+EBV+SOF	4	31	TN	Overall		SVR4/8 39
			26		HCV subtype	GT1a	35
			5		HCV subtype	GT1b	60
			10		IL28B genotype	CC	40
			20			non-CC	35
		6	30		Overall		SVR4/8 87
			26		HCV subtype	GT1a	85
			4			GT1b	100
			8		IL28B genotype	CC non-CC	100
			22				82

SVR12/primary endpoint coding: dark green: 100%; green: 90-99%; yellow: 80-89%; orange: 70-79%; red: <70%.

ASV: asunaprevir; BCV: beclabuvir; DBV: dasabuvir; DCV: daclatasvir; EBV: Epstein-barr virus; GT: genotype; GZV: grazoprevir; HCV: hepatitis C virus; LDV: ledipasvir; OBV: ombitasvir; pegIFN: pegylated-interferon; PI: protease inhibitors; PRV: paritaprevir; RBV: ribavirin; RTV: ritonavir; SMV: simeprevir; SOF: sofosbuvir; SVR4: sustained virologic response at week 4; SVR4/8: sustained virologic response at either 4 or 8 weeks after completing therapy; SVR12: sustained virologic response 12 weeks after completion of therapy; TE: treatment-experienced; TN: treatment-naïve.

Daclatasvir + Sofosbuvir

DCV is the first-in-class NS5A replication complex inhibitor and is a potent and pangenotypic DAA.[9,10] Its pharmacokinetic profile is supportive of once-daily dosing within a well-tolerated safety profile.[11] As DCV has demonstrated a low potential for drug-drug interactions, it is already approved in combination with other DAAs such as SOF in Europe (GT1-4) and asunaprevir in Japan (GT1).

Common patient populations

Genotype 3

Cirrhotic and non-cirrhotic/treatment-experienced and treatment-naïve patients: ALLY-3

The landmark ALLY Phase III programme comprises three studies evaluating the efficacy and safety of an all-oral combination of DCV+SOF in patients with high unmet medical needs: ALLY-1, conducted in GT1-6 patients with cirrhosis or post-liver transplant (n=113) receiving the combination for 12 weeks; ALLY-2, conducted in GT1-6 patients with HIV co-infection and receiving the combination for 8 or 12 weeks; and ALLY-3, in which GT3 treatment-naïve or experienced patients received the combination for 12 weeks.

While ALLY-1 and ALLY-2 are still ongoing, the results for the ALLY-3 study were first presented in a late-breaking abstract of an oral presentation by Nelson et al.[12] at AASLD 2014. In the ALLY-3 clinical trial, the first 12-week Phase III study on such a combination, 152 GT3 patients, either treatment-naïve (n=101) or treatment-experienced (n=52), were enrolled to receive open-label once-daily DCV 60 mg + SOF 400 mg for 12 weeks. This treatment phase led to 24 weeks of follow-up. The cohort of treatment-experienced patients comprised prior treatment failures with SOF or the cyclophilin inhibitor alisporivir (prior treatment with NS5A inhibitors was an exclusion criteria).

90% of treatment-naïve patients and 86% of treatment-experienced patients achieved SVR12 (Table 6). Cirrhosis status (determined by liver biopsy, FibroScan or FibroTest) was associated with lower (63%) SVR12 rates than in non-cirrhotic patients (96%). This influence of cirrhosis was even more marked in the treatment-naïve cohort (97% versus 58%, respectively) than in the treatment-experienced cohort (94% versus 69%, respectively). Higher SVR12 rates were positively associated with female gender, younger patient age (<65 years), HCV RNA levels <800 000 IU/ml, CC-IL28B genotype, and absence of cirrhosis.

Table 4: Key results from studies presented at the American Association for the Study of Liver Disease 2014: GT1 non-cirrhotic patients 2014: GT1 cirrhotic patients.

Study	Treatment arms/subgroups	Duration (weeks)	n	TN/TE	Subgroup 1	Subgroup 2	SVR12 (%) or primary endpoint
GENOTYPE 1							
CIRRHOTIC							
Prospective randomised national study[5]	SOF+RBV	16	4	TN			0
		24	6				33
SIRIUS[19]	SOF/LDV+RBV	12	77	PI-failures			96
	SOF/LDV	24	77				97
SOLAR-1[20]	SOF/LDV+RBV	12	52	TN/TE	GT1a and GT4 (n=3)	Overall	87
			30			CPT B	87
			22			CPT C	86
		24	47		GT1a	Overall	89
			27			CPT B	89
			20			CPT C	90
PHOTON 1 & 2[7]	SOF+RBV	24	22	TN	HIV co-infection		64
HCV-TARGET[14]	SOF+SMV+/-RBV (n=180)	N/A	180	TN/TE			SVR4 87
	SOF+RBV+pegIFN (n=37)		37				SVR4 70

Table 4 continued.

Study	Treatment arms/subgroups	Duration (weeks)	n	TN/TE	Subgroup 1	Subgroup 2	SVR12 (%) or primary endpoint
HCV-TARGET Subanalysis[15]	SOF+SMV+/-RBV (n=37)	N/A	37	TE	Post-transplant		SVR4 86
Pooled analysis[16]	LDV+SOF+/-RBV	12 or 24	513	TN/TE			96
			161	TN			98
			352	TE			95
		12	322	TN/TE			95
			92	TN			97
			230	TE			94
		24	191	TN/TE			98
			69	TN			99
			122	TE			98
	LDV+SOF	12 or 24	251	TN/TE			95
			80	TN			96
			171	TE			95
		12	118	TN/TE			92
			47	TN			96
			71	TE			90
		24	133	TN/TE			98
			33	TN			97
			100	TE			98
	LDV+SOF+RBV	12 or 24	262	TN/TE			97
			81	TN			99
			181	TE			96
		12	204	TN/TE			96
			45	TN			98
			159	TE			96
	LDV+SOF+RBV	24	58	TN/TE			100
			36	TN			100
			22	TE			100
UNITY-2[34]	DCV+ASV+BCV	12	102	TN/TE	Overall		90
			57	TN	Overall		93
			40		HCV subtype	GT1a	90
			17			GT1b	100
			45	TE	Overall		87
			35		HCV subtype	GT1a	86
			10			GT1b	90
	DCV+ASV+BCV+RBV		100	TN/TE	Overall		96
			45	TN	Overall		87
			39		HCV subtype	GT1a	97
			15			GT1b	100
			45	TE	Overall		93
			35		HCV subtype	GT1a	91
			10			GT1b	100
TURQUOISE II[38]	PRV+RTV+OBV+DBV+RBV	12	208	TN/TE	Overall		92

Table 4 continued.

Study	Treatment arms/subgroups	Duration (weeks)	n	TN/TE	Subgroup 1	Subgroup 2	SVR12 (%) or primary endpoint
TURQUOISE II[38]	PRV+RTV+OBV+DBV+RBV	12	35	TN/TE	IL28B genotype	CC	94
			132			CT	95
			41	TN/TE	IL28B genotype	TT	81
			140		HCV subtype	GT1a	89
			68			GT1b	99
			86		Prior pegIFN/RBV experience	Naïve	94
			29			Relapser	97
			18			Partial responder	94
			75			Null responder	87
		24	172		Overall		97
			34		IL28B genotype	CC	97
			105			CT	97
			33			TT	94
			121		HCV subtype	GT1a	95
			51			GT1b	100
			74			Naïve	96
			23		Prior pegIFN/RBV experience	Relapser	100
			13			Partial responder	100
			62			Null responder	95
Pooled analysis from SAPPHIRE-I, SAPPHIRE-II, TURQUOISE-II and PEARL-IV (GT1a)[35]	PRV+RTV+OBV+DBV+RBV, 12 weeks	12	142	TN/TE			89
			66	TN			92
			15	TE	Relapse		93
			11		Partial response		100
			50		Null response		80
		24	121	TN/TE			95
			56	TN			95
			13	TE	Relapse		100
			10		Partial response		100
			42		Null response		93
C-SWIFT[41]	GZV+EBV+SOF	6	20	TN	Overall		SVR4/8 80
			16		HCV subtype	GT1a	81
			4			GT1b	75
			6		IL28B genotype	CC	100
			14			non-CC	71
		8	21		Overall		SVR4/8 95
			15		HCV subtype	GT1a	93
			4			GT1b	100
			5		IL28B genotype	CC	100

Table 4 continued.

Study	Treatment arms/subgroups	Duration (weeks)	n	TN/TE	Subgroup 1	Subgroup 2	SVR12 (%) or primary endpoint
C-WORTHY[42]	GZV+EBV+SOF	8	13	TN	IL28B genotype	non-CC	100
	GZV+EBV	12	29				97
	GZV+EBV+RBV		31				90
	GZV+EBV	18	31				94
	GZV+EBV+RBV		32				97

SVR12/primary endpoint coding: dark green: 100%; green: 90-99%; yellow: 80-89%; orange: 70-79%; red: <70%.
ASV: asunaprevir; BCV: beclabuvir; CPT: Child-Pugh-Turcotte; DBV: dasabuvir; DCV: daclatasvir; EBV: Epstein-barr virus; GT: genotype; GZV: grazoprevir; HCV: hepatitis C virus; LDV: ledipasvir; OBV: ombitasvir; pegIFN: pegylated-interferon; PI: protease inhibitors; PRV: paritaprevir; RBV: ribavirin; RTV: ritonavir; SMV: simeprevir; SOF: sofosbuvir; SVR4: sustained virologic response at week 4; SVR4/8: sustained virologic response at either 4 or 8 weeks after completing therapy; SVR12: sustained virologic response 12 weeks after completion of therapy; TE: treatment-experienced; TN: treatment-naïve.

Overall, the combination was relatively safe and well tolerated. Most frequently reported (≥10%) AEs included headache, fatigue, and nausea. No deaths, treatment-related serious AEs, or discontinuations due to AEs were reported during the course of the study. In conclusion, the DCV+SOF combination demonstrated high SVR rates in both treatment-naïve and treatment-experienced non-cirrhotic GT3 patients after only 12 weeks. Unfortunately, the group with the most unmet medical needs with cirrhosis did not do very well on DCV and SOF and 12 weeks without RBV is inadequate for these patients. These results follow those of an open-label randomised study on GT1-3 patients receiving DCV+SOF with or without RBV, and in which 89% of GT3 patients achieved an SVR12 but after a treatment duration of 24 weeks,[13] and with no impact of addition of RBV or of a lead-in phase with SOF.

Multiple Sofosbuvir-Based Regimens: Real-World Data

HCV-TARGET[4,14] is a longitudinal observational cohort study conducted in 53 centres in the US, Germany, and Canada, with the aim of investigating current practices and use of DAAs so as to evaluate real-world data and determine their correlation with Phase III study results. Among all patients initiated with SOF-based regimens (n=2,063), most GT1 patients were given SOF+SMV therapy, with (14.9%) or without (53.1%) RBV, the remaining GT1 patients were either treated with SOF+pegylated-interferon (peg-IFN)+RBV (23.1%) or with SOF+RBV (8.8%). GT2 patients were almost exclusively (99.1%) treated with SOF+RBV regimens, while 91.5% of GT3 patients were given SOF+RBV and 8.5% received triple combination therapy with SOF+pegINF+RBV.

Among GT1 and GT2 patients, high (85% and over) SVR at post-treatment week 4 (SVR4) rates were achieved regardless of RBV presence or cirrhosis status, except for GT1 cirrhotic patients treated with SOF+RBV+pegIFN who achieved a lower SVR rate (70%; Tables 2-5). At the time of the presentation clinical outcomes on GT3 patients were not available as these patients were still being followed-up due to longer treatment. In this population, SOF-based regimens appeared to be safe and well tolerated, with minimal discontinuation rates due to AEs. AE occurrence was lower in regimens of SOF+SMV +/- RBV versus SOF+pegINF+RBV and SOF+RBV, the most frequently reported AEs being fatigue, headache, and nausea. At AASLD 2014, interval results from the study were also presented for patients (n=227) in the post-transplant setting.[15]

Among GT1 patients, 61.8% were given SOF+SMV while 17.9%, 13.4%, and 7.3% received SOF+SMV+RBV, SOF+RBV+pegINF, and SOF+RBV regimens, respectively. 100% of GT2 patients received SOF+RBV while 94.7% and 5.3% of GT3 patients were

treated with SOF+RBV and SOF+RBV+pegINF, respectively. High crude SVR4 rates were achieved, such as 90% for GT1 patients treated with SOF+SMV+/-RBV, 83% for GT1 patients treated with SOF+RBV+pegINF, and 90% in GT2 patients. GT3 patients who received SOF+RBV and SOF+RBV+pegINF achieved crude SVR4 rates of 60% and 100%, respectively (Tables 2-6).

Ledipasvir + Sofosbuvir

Ledipasvir (LDV) is a NS5A inhibitor with picomolar potency against HCV GT1a/b that is currently approved in Europe and in the US in a fixed-dose combination (FDC) with SOF.

Common patient populations

Genotype 1

Compensated cirrhosis/treatment-experienced and treatment-naïve patients

Bourlière et al.[16] presented the results of a pooled analysis from Phase II/III clinical trials on LDV/SOF regimens in GT1 patients (treatment-naïve or treatment-experienced) with compensated cirrhosis (n=513). High SVR12 rates were achieved in all subgroups regardless of HCV genotype, and did not differ according to baseline characteristics (Table 4). The overall SVR12 rate was 96%, and was positively associated with longer treatment duration. However, these results seemed to be driven by the subgroup of treatment-experienced patients where 12 weeks of LDV/SOF without RBV was associated with a significant drop in SVR12. This is reflected by international guidelines, which recommend either the addition of RBV or treatment extension to 24 weeks in treatment-experienced cirrhotic GT1 patients.[6] However, SVR12 rates were lower among cirrhotic patients according to FibroTest+APRI and patients with a platelet count <75,000/mm^3. Safety outcomes were comparable with those reported in previous clinical studies, with a higher incidence of AEs and haemoglobin declines in RBV-containing regimens.

Genotypes 3 and 6

In a Phase II multicentre, open-label study,[17] 50 treatment-experienced GT3 patients and 25 GT6 treatment-naïve or treatment-experienced patients were evaluated to assess the efficacy and safety of a 12-week regimen of LDV/SOF+RBV and LDV/SOF, respectively. 44% and 8% of GT3 and GT6 patients were cirrhotic, respectively. High SVR12 rates (≥82%) were observed in all patient subgroups, especially in GT6 patients (96%). However, the lowest rate was observed in the GT3 cirrhotic subgroup (73%; Tables 6 and 9). The combination was reported as safe in all subgroups, and could be considered an attractive all-oral treatment option in GT6 patients.

Specific patient populations

Genotype 1 salvage therapy

Relapsing patients following SOF-based therapy/cirrhotic and non-cirrhotic/treatment experienced patients

The combination of LDV/SOF+RBV for a treatment duration of 12 weeks was evaluated in a single-arm prospective Phase II trial on 51 GT1 patients who failed previous SOF-based treatment, and preliminary results were presented at AASLD 2014.[18] The overall SVR12 rate was of 98%, but the single patient in the study who relapsed was found to be GT3a and should not have been enrolled; consequently, the SVR12 in the 50 GT1 patients was of 100% (Table 2). Retreatment with LDV/SOF+RBV was generally safe, with no deaths reported, but two patients experienced serious AEs (bipolar disorder, which led to study discontinuation, and concomitant chest pain associated with anaemia and cholecystitis). Additional arms of the study are still ongoing, namely 24-week courses of LDV/SOF in patients who failed previous treatment with LDV/SOF or LDV/SOF+RBV in patients with advanced liver disease who failed SOF-based therapy.

Cirrhosis

Compensated cirrhosis and multiple failures to pegIFN/RBV and 1st generation protease inhibitor

Bourlière et al. presented the results of the randomised, double blind Phase II SIRIUS trial in which the LDV/SOF FDC (with [combination for 12 weeks, n=77] or without RBV [placebo RBV, combination for 24 weeks, n=77]) was investigated in a population of 154 GT1 patients with compensated cirrhosis and who had previously failed to achieve SVR following pegIFN/RBV and a first-generation protease inhibitor.[19] 97% of patients achieved SVR12 and similar SVR12 rates were observed after 12 weeks of LDV/SOF+RBV (96%) compared to 24 weeks of LDV/SOF (97%; Table 4). Overall, LDV/SOF+/-RBV was safe and well tolerated with the majority of AEs being of mild to moderate severity.

Table 5: Key results from studies presented at the American Association for the Study of Liver Disease 2014: GT2 patients.

Study	Treatment arms/subgroups	Duration (weeks)	n	TN/TE	Subgroup 1	Subgroup 2	SVR12 (%) or primary endpoint
GENOTYPE 2							
OVERALL POPULATION							
PHOTON 1 & 2[7]	SOF+RBV	12	45	TN	HIV co-infection		89
		24	30	TE			90
HCV-TARGET[14]	SOF+RBV	N/A	187	TN/TE	Post-transplant		SVR4 90
HCV-TARGET subanalysis[15]	SOF+RBV	N/A	10	TE			SVR4 90
NON-CIRRHOTIC							
PHOTON 1 & 2[7]	SOF+RBV	12	43	TN	HIV co-infection		88
		24	24	TE			88
SOF+GS-5816 Part A[27,28]	SOF+GS-5816 25 mg	12	11	TN			91
	SOF+GS-5816 100 mg		10				100
SOF+GS-5816 Part B[27]	SOF+GS-5816 25 mg	8	26	TN			77
	SOF+GS-5816 25 mg +RBV		25				88
	SOF+GS-5816 100 mg		26				88
	SOF+GS-5816 100 mg +RBV		26				88
HCV-TARGET[14]	SOF+RBV	N/A	128	TN/TE			SVR4 91
CIRRHOTIC							
PHOTON 1 & 2[7]	SOF+RBV	12	2	TN	HIV co-infection		100
		24	6	TE			100
HCV-TARGET[14]	SOF+RBV	N/A	59	TN/TE			SVR4 88
HCV-TARGET subanalysis[15]	SOF+RBV	N/A	10	TE	Post-transplant		SVR4 90

SVR12/primary endpoint coding: dark green: 100%; green: 90-99%; yellow: 80-89%; orange: 70-79%; red: <70%.
RBV: ribavirin; SOF: sofosbuvir; SVR4: sustained virologic response at week 4; SVR12: sustained virologic response 12 weeks after completion of therapy; TE: treatment-experienced; TN: treatment-naïve; HCV: hepatitis C virus.

Decompensated cirrhosis

The combination of LDV/SOF+RBV was also explored in the multicentre prospective SOLAR-1 study conducted in 108 GT1 or GT4 patients with decompensated cirrhosis (Child-Pugh-Turcotte [CPT] Class B or C).[20] Patients were randomised to receive either 12 (n=52) or 24 weeks (n=47) of therapy: preliminary results were presented at AASLD 2014. Overall, relapse rates were similar to those observed in patients with compensated cirrhosis: 87% and 89% of patients treated for 12 or 24 weeks respectively achieved SVR12, or continued undetectable HCV viral load 12 weeks after completing therapy (which is considered a cure). SVR12 rates at 12 and 24 weeks were similar for patients with CPT Class B (87% and 89%) and Class C (86% and 90%), highlighting the fact that extending treatment duration to 24 weeks might not be required in this patient population (Table 4).

Moreover, concurrent improvements to the virologic response were observed with respect to bilirubin and albumin levels as well as model

for end-stage liver disease and CPT scores in both CPT classes. The combination was generally safe and well tolerated, but 28% of patients experienced a serious AE, which is not surprising in this fragile population. In conclusion, these results represent a significant step forward in a patient population for which there is currently no approved standard of care, and that is deemed a priority by experts in the field.

Table 6: Key results from studies presented at the American Association for the Study of Liver Disease 2014: GT3 patients.

Study	Treatment arms/ subgroups	Duration (weeks)	n	TN/TE	Subgroup 1	Subgroup 2	SVR12 (%) or primary endpoint
GENOTYPE 3							
OVERALL POPULATION							
ALLY-3 Phase III trial[12]	DCV+SOF	12	101	TN			90
			51	TE			86
Prospective randomised national study[5]	SOF+RBV	16	30	TN			87
		24	31				90
PHOTON 1 & 2[7]	SOF+RBV	12	42	TN	HIV co-infection		67
		24	57	TN			91
		24	66	TE			88
HCV-TARGET subanalysis[15]	SOF+RBV	N/A	5	TE	Post-transplant		SVR4 60
	SOF+RBV+pegINF		1				SVR4 100
Phase II multicentre, open-label study[17]	LDV+SOF+RBV	12	50	TE			82
NON-CIRRHOTIC							
ALLY-3 Phase III trial[12]	DCV+SOF	12	109	TN/TE			96
			75	TN			97
			34	TE			94
PHOTON 1 & 2[7]	SOF+RBV	12	36	TN	HIV co-infection		67
		24	54	TN			91
		24	37	TE			95
Prospective randomised national study[5]	SOF+RBV	16	24	TN			88
		24	26				96
Phase II study[29]	SOF+GS-5816 25 mg	12	26	TE			85
	SOF+GS-5816 25 mg +RBV		28				96
	SOF+GS-5816 100 mg		27				100
	SOF+GS-5816 100 mg +RBV		26				100
ELECTRON-2[30]	SOF+GS-5816 25 mg	12	27	TN			100
	SOF+GS-5816 100 mg		27				96
	SOF+GS-5816 25 mg +RBV		24				88
	SOF+GS-5816 100 mg +RBV		26				100
Phase II multicentre, open-label study[17]	LDV+SOF+RBV	12	28	TE			89
CIRRHOTIC							
ALLY-3 Phase III trial[12]	DCV+SOF	12	32	TN/TE			63

Table 6 continued.

Study	Treatment arms/ subgroups	Duration (weeks)	n	TN/TE	Subgroup 1	Subgroup 2	SVR12 (%) or primary endpoint
ALLY-3 Phase III trial[12]	DCV+SOF	12	19	TN			58
			13	TE			69
PHOTON 1 & 2[7]	SOF+RBV	12	6	TN	HIV co-infection		67
		24	3	TN			100
		24	29	TE			79
Prospective randomised national study[5]	SOF+RBV	16	6	TN			83
	SOF+RBV	24	5				60
SOF+GS-5816 Part A[27,28]	SOF+GS-5816 25 mg	12	26	TE			58
	SOF+GS-5816 25 mg +RBV		25				84
	SOF+GS-5816 100 mg		26				88
	SOF+GS-5816 100 mg +RBV		26				96
Phase II multicentre, open-label study[17]	LDV+SOF+RBV	12	22	TE			73

SVR12/primary endpoint coding: dark green: 100%; green: 90-99%; yellow: 80-89%; orange: 70-79%; red: <70%.

LDV: ledipasvir; pegIFN: pegylated-interferon; RBV: ribavirin; SOF: sofosbuvir; SVR4: sustained virologic response at week 4; SVR12: sustained virologic response 12 weeks after completion of therapy; TE: treatment-experienced; TN: treatment-naïve; HCV: hepatitis C virus.

Sofosbuvir + GS-5816

GS-5816 is an investigative NS5A inhibitor with pangenotypic activity, as demonstrated by a previous monotherapy study, and pharmacokinetic properties supporting once-daily dosing.[21] It is currently under evaluation in several Phase III clinical studies (namely the ASTRAL trials) in combination with SOF.[22-26]

Common patient populations

Genotypes 1-6

Non-cirrhotic/treatment-naïve patients: Phase II open-label study

In another Phase II open-label study,[27] the once-daily combination of 400 mg SOF plus 25/100 mg GS-5816 +/- RBV was evaluated for efficacy and safety outcomes. 154 treatment-naïve, non-cirrhotic patients from three cohorts (GT1 [n=55], GT3 [n=54] and GT 2,4-6 [n=45]) were enrolled. In Part A, patients were randomised 1:1 to SOF+GS-5816 25 mg or SOF+GS-5816 100 mg for 12 weeks (results were presented at the 2014 International Liver Congress [ILC] meeting; Tables 3, 5-7).[28] In Part B (n=223), only GT1 (n=120) and GT2 (n=103) patients were randomised 1:1:1:1 to SOF+GS-5816 25 mg, SOF+GS-5816 25 mg+RBV, SOF+GS-5816 100 mg, or SOF+GS-5816 100 mg+RBV for 8 weeks.[27] 96% and 100% of G1 patients from the 25 mg and 100 mg treatment arms achieved an SVR12, respectively (Table 3). Similarly, every SVR12 rate for genotypes 2-6 was higher than 86% (Tables 5-7).

In Part B, utilising an 8 week regimen, SVR12 rates of SOF+GS-5816 with or without RBV in GT1 and GT2 patients were lower than that previously reported for 12 weeks, with rates ranging from 77 to 90%. Therefore, this combination will be further explored in Phase III studies for a treatment duration of 12 weeks. Most AEs were low grade and of mild intensity and the treatment was well tolerated.

Genotypes 1 and 3

Cirrhotic and non-cirrhotic/ treatment-experienced patients

In a Phase II study,[29] the once-daily combination of 400 mg SOF+GS-5816 25 mg or 100 mg +/- RBV

was evaluated across three cohorts consisting of treatment-experienced GT3 patients without (Cohort 1, n=107) or with cirrhosis (Cohort 2, n=103), and GT1 patients with prior failures to protease inhibitor regimens with or without cirrhosis (Cohort 3, n=111). In all three cohorts patients were randomised 1:1:1:1 to SOF+GS-5816 25 mg, SOF+GS-5816 25 mg + RBV, SOF+GS-5816 100 mg or SOF+GS-5816 100 mg + RBV for 12 weeks.

All GT3 non-cirrhotic patients (100%) within the SOF+GS-5816 100 mg and SOF+GS-5816 100 mg + RBV arms (Cohort 1) reached SVR12, while 85% and 96% of GT3 patients who received SOF+GS-5816 25 mg without or with RBV reached SVR12, respectively (Table 6). In the second cohort of GT3 cirrhotic patients, 88% and 96% of patients from the SOF+GS-5816 100 mg and SOF+GS-5816 100 mg + RBV arms reached SVR12, respectively, while 58% and 84% of patients who received SOF+GS-5816 25 mg without or with RBV reached SVR12, respectively (Table 6). All (100%) GT1 patients with RBV-free regimens (GS-5816 25 mg or 100 mg) reached SVR12, while 97% and 96% of patients reached SVR12 with RBV-containing regimens, respectively (Table 2).

Overall, the regimens were well tolerated with low incidences of serious AEs or discontinuation. However, RBV co-administration was positively correlated to increased incidence of pruritus and rash. The authors concluded that RBV co-administration does not yield additional benefits and that 100 mg regimens of GS-5816 are superior to 25 mg regimens. As a consequence, SOF 400 mg and GS-5810 100 mg have been co-formulated in a FDC for Phase III investigation.

Table 7: Key results from studies presented at the American Association for the Study of Liver Disease 2014: GT4-5-6 patients.

Study	Treatment arms/ subgroups	Duration (weeks)	n	TN/TE	Subgroup 1	Subgroup 2	SVR12 (%) or primary endpoint
GENOTYPE 4							
OVERALL POPULATION							
PHOTON 1 & 2[7]	SOF+RBV, 24 weeks (n=31)	24	31	TN	HIV co-infection		84
NON-CIRRHOTIC							
PHOTON 1 & 2[7]	SOF+RBV, 24 weeks	24	23	TN	HIV co-infection		83
SOF+GS-5816 Part A[27,28]	SOF+GS-5816 25 mg	12	7	TN			100
	SOF+GS-5816 100 mg		7				86
CIRRHOTIC							
PHOTON 1 & 2[7]	SOF+RBV, 24 weeks	24	8	TN	HIV co-infection		88
GENOTYPE 5							
OVERALL POPULATION							
SOF+GS-5816 Part A[27,28]	SOF+GS-5816 25 mg	12	1	TN			100
GENOTYPE 6							
OVERALL							
Phase II multicentre, open-label study[17]	LDV+SOF+RBV	12	25	TN/TE			96
NON-CIRRHOTIC							
SOF+GS-5816 Part A[27,28]	SOF+GS-5816 25 mg	12	4	TN			100
	SOF+GS-5816 100 mg	12	5				100

LDV: ledipasvir; RBV: ribavirin; SOF: sofosbuvir; SVR12: sustained virologic response 12 weeks after completion of therapy; TE: treatment-experienced; TN: treatment-naïve.

Genotype 3

Non-cirrhotic/treatment-naïve patients: ELECTRON-2

At AASLD 2014, Gane et al.[30] presented the Phase II open-label ELECTRON-2 study which evaluated the 8-week once-daily combination of SOF + 25/100 mg GS-5816 (+/- RBV) in treatment-naïve non-cirrhotic GT3 patients (n=104). The main clinical endpoint, SVR12 (lower limit of quantification, 15 IU/ml), reached 100% in the SOF + 25 mg GS-5816 once daily without RBV arm and the SOF + 100 mg GS-5816 once daily plus RBV arm. SVR12 rates in the SOF + 100 mg GS-5816 once daily without RBV arm and the SOF + 25 mg GS-5816 once daily with RBV arm were of 96% and 88%, respectively (Table 6). No advantage of the addition of RBV was identified in efficacy over combination with SOF and GS-5816 only. Overall, the combination was well tolerated; most frequently reported (≥10%) AEs included fatigue, headache, and nausea. No deaths were reported during the course of the study.

DACLATASVIR + ASUNAPREVIR + BECLABUVIR REGIMENS

Asunaprevir (ASV) is an investigational NS3 protease inhibitor, while beclabuvir (BCV) is an investigational non-nucleoside NS5B polymerase inhibitor; both are active against GT1 and GT4. The DCV+ASV+BCV combination therapy is currently under investigation. In Phase II studies, this triple combination achieved SVR12 rates of 92% and 100% in GT1 and GT4 treatment-naïve patients, respectively, and was co-formulated into an oral single FDC taken twice daily (BID).[31,32]

Common Patient Populations

Genotype 1

Non-cirrhotic/treatment-experienced and treatment-naïve patients: UNITY-1

In a multicentre, non-randomised, open-label Phase III trial, the safety and efficacy of the BID FDC of DCV+ASV+BCV as a 12-week regimen was explored in 415 GT1 non-cirrhotic treatment-naïve and treatment-experienced patients.[33] The overall SVR12 rate was of 91%; comparable SVR12 rates were observed between treatment-naïve and treatment-experienced patients (Table 2-4). However, a difference in SVR12 was detected between GT1a and GT1b patients. The triple combination was relatively safe and well tolerated overall, with low rates of serious AEs and discontinuations due to AEs. Of note, alanine aminotransferase (ALT) elevations (5 times the upper limit) were reported in five patients.

Compensated cirrhosis/treatment-experienced and treatment-naïve patients: UNITY-2

In a multicentre, randomised, double-blind Phase III trial, 202 GT1 patients with compensated cirrhosis were assessed for efficacy and safety parameters following randomisation to a 12-week regimen with a BID FDC with DCV+ASV+BCV with (n=100) or without (n=102) RBV.[34] Patients were stratified by treatment history (treatment-naïve [n=112] or treatment experienced [n=90]). Overall, the SVR12 rates in the DCV+ASV+BCV and DCV+ASV+BCV+RBV were of 93% and 98%, respectively (Table 4). In all subgroups, high (≥87%) SVR12 rates were observed, with a positive association with treatment-naïve versus treatment-experienced patients. The addition of RBV was positively associated with higher SVR12 and lower relapse rates. The triple combination, with or without RBV, was relatively safe and well tolerated overall, although the RBV arm was associated with higher AE occurrences and discontinuations. One patient who had achieved SVR12 discontinued all treatment due to anaemia, ALT elevation (5 times the upper limit), and total bilirubin elevation (2.5 times the upper limit).

PARITAPREVIR + RITONAVIR + OMBITASVIR + DASABUVIR +/- RIBAVIRIN REGIMENS

AbbVie '3D' is a combination comprising paritaprevir (PRV; formerly ABT-450), ritonavir (RTV), and ombitasvir (OBV) co-formulated in one single pill (two pills once daily), and twice-daily dasabuvir (DBV), with or without RBV, and was recently approved in the US and Europe for genotype 1/4 patients.

Common Patient Populations

Genotype 1a

Cirrhotic and non-cirrhotic/treatment-experienced and treatment-naïve patients: pooled data from the SAPPHIRE-I, SAPPHIRE-II, TURQUOISE-II AND PEARL-IV Phase III studies

Everson et al.[35] presented the results of a retrospective analysis of pooled data from the

Phase III SAPPHIRE-I, SAPPHIRE-II, TURQUOISE-II, and PEARL-IV studies in which GT1a patients received PRV+RTV+OBV+DBV+/-RBV (n=1,058). In non-cirrhotic patients, higher SVR12 rates were observed in RBV-containing cohorts (96% versus 90%; p<0.05), as well as in cirrhotic patients (95% versus 89%; Tables 3 and 4). In non-cirrhotic patients, lower SVR12 rates were associated with high body mass index (BMI) (odds ratio: 0.90 [95% confidence interval: 0.84-0.97]; p=0.005). Longer treatment duration (24 versus 12 weeks) showed the greatest benefit in cirrhotic patients who were previous null responders.

In cirrhotic patients, lower SVR12 rates were significantly associated with IL28B TT genotype (p=0.008), previous null response (p=0.009), history of injection drug use (0.047), and treatment in North America (versus Europe; p=0.045). As previously reported in earlier studies, the safety profiles of the regimens were acceptable, with low rates of discontinuation due to AEs and no differences between the 12 and 24-week modalities; however, addition of RBV was associated with higher AE occurrence.

Genotype 1

Cirrhotic/DAA-naïve patients: TURQUOISE-II subanalysis

In the TURQUOISE open-label Phase III trial, the PRV+RTV+OBV+DBV+RBV combination was evaluated in 380 GT1 DAA-naïve cirrhotic patients, a challenging population, for 12 (n=208) or 24 (n=172) weeks.[36] SVR12 rates in the overall cohorts, as presented at the 2014 ILC and subsequently published, were 92% and 97% after 12 and 24 weeks of treatment, respectively (Table 4).[37] In a subanalysis presented at AASLD 2014, the impact of baseline demographic, viral, and disease characteristics was evaluated with respect to treatment outcomes in patients with compensated cirrhosis.[38]

High SVR12 rates were observed, regardless of most viral, demographic, and disease factors (age, gender, race, BMI, diabetes, injection drug use, baseline HCV RNA, albumin, and platelets). However, following logistic regression analyses, IL28B TT genotype, previous null response to pegIFN/RBV, and GT1a HCV were significantly associated with decreased probability of SVR12. The safety profile was similar to those observed in other clinical trials of the five-drug regimen, with low rates of discontinuation due to AEs.

GRAZOPREVIR + ELBASVIR +/- SOFOSBUVIR +/- RIBAVIRIN REGIMENS

Grazoprevir (formerly MK-5172) is an investigational NS3/4A protease inhibitor, while elbasvir (formerly MK-8742) is an investigational NS5A inhibitor. Their combination, with or without RBV, has previously demonstrated high virologic results in treatment-naïve GT1 patients, as well as GT1 previous null responders with or without cirrhosis.[39,40]

Common Patient Populations

Genotype 1

Cirrhotic and non-cirrhotic/treatment-naïve patients: C-SWIFT

At AASLD 2014 Lawitz et al.[41] presented the results of the interim analysis of C-SWIFT, an open-label Phase II trial evaluating the efficacy and safety of the triple FDC of grazoprevir, elbasvir, and SOF in 102 treatment-naïve GT1 patients. The study comprised non-cirrhotic (n=61) and cirrhotic (n=41) patients who received this treatment for 4 or 6 weeks (non-cirrhotics), and 6 or 8 weeks (cirrhotics). Evaluation in GT3 is also included in this study but is still ongoing: therefore, results were not reported. High SVR rates at either 4 or 8 weeks after completing therapy (SVR4/8) were observed in the 6 and 8-week therapy arms, with a positive correlation for patients with GT1b, IL28B CC genotype, or lower baseline HCV RNA levels (Tables 3 and 4). Conversely, a high rate of relapse was observed in the 4-week arm (SVR12, 39%). The FDC was well tolerated overall, with only one patient discontinuing the study due to an AE, which was unrelated to the study drug.

Cirrhotic and non-cirrhotic/treatment-experienced and treatment-naïve patients: C-WORTHY

Lawitz et al.[42] presented the final results from the randomised Phase IIb clinical program C-WORTHY, which evaluated grazoprevir and elbasvir as a combination with or without RBV for treatment durations of 12-18 weeks in GT1 patients. The study evaluated this combination in two GT1 cohorts (n=253): treatment-naïve cirrhotic patients (n=123) and treatment-experienced patients who were null responders to peg-IFN or RBV (n=130). High response rates were observed in both populations, with SVR12 rates of 90-97% in the treatment-naïve cohort and 91-100% in previous null responders with or without cirrhosis. These high SVR12s

were observed regardless of RBV combination or treatment duration. In both arms the treatment was well tolerated, with 1% of patients discontinuing due to AEs; the most commonly reported being fatigue, headache, and asthenia.

CONCLUSION

Following the strengthening of the new era of DAAs, the main objective for clinicians managing hepatitis C patients is to bring high cure rates with acceptable toxicities. Nevertheless, some patient subpopulations still represent a challenge yet to be addressed, and are a clear unmet medical need, especially with associated comorbidities or challenging clinical settings (for instance advanced liver disease, pre and post-transplant patients, and HIV/HCV co-infected patients).[1] The 2014 AASLD meeting provided further insight into these patient subpopulations, which will certainly help clinicians select the most appropriate regimen for patients.

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18. Wyles DL et al. Retreatment of patients who failed prior sofosbuvir-based regimens with all oral fixed-dose combination ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Abstract 235. 65th Annual Meeting of the American

Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.

19. Bourlière M et al. Ledipasvir/sofosbuvir fixed-dose combination is safe and efficacious in cirrhotic patients who have previously failed protease-inhibitor based triple therapy. Abstract LB-6. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.

20. Flamm SL et al. Ledipasvir/sofosbuvir with ribavirin for the treatment of HCV in patients with decompensated cirrhosis: preliminary results of a prospective, multicenter study. Abstract 239. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.

21. Lawitz E et al. GS-5816, a once-daily NS5A inhibitor, demonstrates potent antiviral activity in patients with genotype 1-4 HCV infection in a 3 day monotherapy study. Abstract 1082. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Washington, DC, USA, 1-5 November 2013.

22. Gilead Sciences. Sofosbuvir/GS-5816 fixed dose combination for 12 weeks in adults with chronic HCV infection (ASTRAL-1). NCT02201940. https://clinicaltrials.gov/ct2/show/NCT02201940.

23. Gilead Sciences. Sofosbuvir/GS-5816 fixed-dose combination in adults with chronic HCV infection. NCT02346721. https://clinicaltrials.gov/ct2/show/NCT02346721.

24. Gilead Sciences. Comparison of Sofosbuvir/GS-5816 fixed dose combination for 12 weeks with sofosbuvir and ribavirin for 12 weeks in adults with chronic genotype 2 HCV infection (ASTRAL-2). NCT02220998. https://clinicaltrials.gov/ct2/show/NCT02220998.

25. Gilead Sciences. Comparison of Sofosbuvir/GS-5816 fixed dose combination for 12 weeks with sofosbuvir and ribavirin for 24 weeks in adults with chronic genotype 3 HCV infection (ASTRAL-3). NCT02201953. https://clinicaltrials.gov/ct2/show/NCT02201953.

26. Gilead Sciences. Sofosbuvir/GS-5816 Fixed-dose combination in adults with chronic HCV infection and Child-Pugh Class B cirrhosis (ASTRAL-4). NCT02201901. https://clinicaltrials.gov/ct2/show/NCT02201901.

27. Tran TT et al. Safety and efficacy of treatment with sofosbuvir + GS-5816 ± ribavirin for 8 or 12 weeks in treatment-naïve patients with genotype 1-6 HCV infection. Abstract 80. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.

28. Everson GT et al. Safety and efficacy of treatment with the interferon-free, ribavirin-free combination of sofosbuvir + GS-5816 for 12 weeks in treatment-naïve patients with genotypes 1-6 HCV infection. Abstract O111. The International Liver Congress 2014, London, United Kingdom, 9-13 April.

29. Pianko S et al. High efficacy of treatment with sofosbuvir + GS-5816 ± ribavirin for 12 weeks in treatment experienced patients with genotype 1 or 3 HCV infection. Abstract 197. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.

30. Gane EJ 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 ELECTRON-2 study. Abstract 79. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.

31. Everson GT et al. Phase 2b study of the interferon-free and ribavirin-free combination of daclatasvir, asunaprevir, and BMS-791325 for 12 weeks in treatment-naive patients with chronic HCV genotype 1 infection. Abstract LB-1. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Washington, DC, USA, 1-5 November 2013.

32. Hassanein T et al. All-oral therapy with daclatasvir in combination with asunaprevir and BMS-791325 for treatment-naive patients with chronic HCV genotype 4 infection. Abstract P1163. The International Liver Congress 2014, London, United Kingdom, 9-13 April.

33. Poordad F et al. All-oral, fixed-dose combination therapy with daclatasvir/asunaprevir/beclabuvir for non-cirrhotic patients with chronic HCV genotype 1 infection: UNITY-1 phase 3 SVR12 results. Abstract LB-7. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.

34. Muir AJ et al. All-oral fixed-dose combination therapy with daclatasvir/asunaprevir/beclabuvir, ± ribavirin, for patients with chronic HCV genotype 1 infection and compensated cirrhosis: UNITY-2 phase 3 SVR12 results. Abstract LB-2. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.

35. Everson GT et al. Integrated efficacy analysis of four phase 3 studies in HCV genotype 1a-infected patients treated with ABT-450/r/ombitasvir and dasabuvir with or without ribavirin. Abstract 83. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.

36. Poordad F et al. TURQUOISE-II: SVR12 rates of 92%-96% in 380 hepatitis C virus genotype 1-infected adults with compensated cirrhosis treated with ABT-450/r/ABT-267 and ABT-333 plus ribavirin (3D+RBV). Abstract O163. The International Liver Congress 2014, London, United Kingdom, 9-13 April.

37. Poordad F et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014 May 22;370(21):1973-82.

38. Fried MW et al. TURQUOISE-II: regimens of ABT-450/r/ombitasvir and dasabuvir with ribavirin achieve high SVR12 rates in HCV genotype 1-infected patients with cirrhosis, regardless of baseline characteristics. Abstract 81. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.

39. Hezode C et al. Safety and efficacy of the all-oral regimen of MK-5172/MK-8742 ± ribavirin in treatment-naive, non-cirrhotic, patients with hepatitis C virus genotype 1 infection: the C-WORTHY study. Abstract 10. The International Liver Congress 2014, London, United Kingdom, 9-13 April.

40. Lawitz E et al. Efficacy and safety of MK-5172 and MK-8742 ± ribavirin in hepatitis C genotype 1 infected patients with cirrhosis or previous null-response: the C-WORTHY study. Abstract O61. The International Liver Congress 2014, London, United Kingdom, 9-13 April.

41. Lawitz E et al. C-SWIFT: Grazoprevir (MK-5172) + Elbasvir (MK-8742) + sofosbuvir in treatment-naive patients with hepatitis C virus genotype 1 infection, with and without cirrhosis, for durations of 4, 6, or 8 weeks (interim results). Abstract LB-33. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.

42. Lawitz E et al. Efficacy and safety of MK-5172 and MK-8742 ± ribavirin in hepatitis C genotype 1 infected patients with cirrhosis or previous null response: final results of the C-WORTHY study (Parts A and B). Abstract 196. 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Boston, Massachusetts, USA, 7-11 November 2014.