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International Liver Congress 2014 Meeting Highlights

INTERNATIONAL LIVER CONGRESS 2014 MEETING HIGHLIGHTS

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ABSTRACT

The main objective of chronic hepatitis C virus (HCV) management is to provide high viral eradication rates with acceptable toxicity. The new era of direct-acting antivirals (DAAs) has considerably changed the standard of care, and each main congress provides new and insightful information. Very encouraging clinical data on interferon and ribavirin-free combinations with oral DAAs were recently made available, and comprise over 90%, and up to 100%, of infection cure rates for treatment-naïve patients; consistent results can also be observed across many difficult-to-cure subpopulations such as patients with advanced liver disease, HIV-coinfected patients, and patients in the post-liver transplant setting, which could, therefore, no longer be considered as difficult-to-cure populations. This review will summarise the highlights of the 2014 International Liver Congress that took place from 9th-13th April in London, UK, and will provide an outlook on the future of HCV treatment.

Keywords: European Association for the Study of the Liver (EASL), International Liver Congress (ILC), chronic hepatitis C, direct acting antivirals, meeting highlights.

INTRODUCTION

2014 is certainly proving to be an exciting year for clinicians managing chronic hepatitis C virus (HCV) patients. Recent developments in clinical research have led to the current era of direct-acting antivirals (DAAs); combinations of these new compounds offer shorter treatment duration, higher infection cure rates, and fewer side-effects than the standard of care therapies based on interferon (IFN)-alpha, therefore changing the treatment paradigm. Very encouraging clinical trial data on IFN and ribavirin (RBV)-free combinations with oral DAAs were recently made available and show infection cure rates of >90%, often approaching 100% for treatment-naïve patients. Comparable results were also observed across many difficult-to-cure subpopulations such as patients with advanced liver disease, HIV co-infection, response failure to IFN-based therapies, or patients in the post-liver transplantation setting. Consequently, all-oral treatment fixed-dose-combinations (FDCs) of DAAs should be available by the end of 2014.

Although the value of these important steps are, to some degree, tempered by the problems of availability due to the costs of the new therapies and the need for large-scale screening, particularly for developing countries, the 2014 International

Liver Congress (ILC) meeting led to optimism that major reductions in the disease burden due to HCV are in sight. The newly-published guidelines from the European Association for the Study of the Liver (EASL) and the World Health Organization highlight these major changes. The meeting highlighted large scale, Phase III pivotal trials that allowed clinicians and patients to examine the detailed data from these pivotal trials (Table 1). This review will summarise the highlights of this meeting so that an outlook can be provided on the future of HCV treatment.

LEDIPASVIR/SOFOSBUVIR

Sofosbuvir (SOF) is a nucleotide analogue inhibitor of HCV polymerase which is active in all HCV genotypes (GTs) and is already approved in Europe and in the US. Ledipasvir (LDV) is a nonstructural protein 5A (NS5A) inhibitor with picomolar potency against HCV GT1a/b. New clinical data from large combination studies involving SOF and LDV in patients infected with GT1 HCV were presented at the 2014 ILC, and useful SOF-based regimen data were also made available in several interesting populations (Table 2).

Table 1: Key clinical studies presented at the 2014 ILC.

Patient characteristics	Previous therapy	Subpopulation	HCV GT	Study name/ Reference	Type of study	Investigated compounds	Treatment duration	N
Non-cirrhotic patients	Treatment-naïve		All	[9]	Open-label Phase II study	SOF + GS-5816	12 weeks	154
			GT1	ION-3[3,4]	Randomised, open-label Phase III trial	LDV/SOF +/- RBV	8 vs 12 weeks	647
			GT1	SAPPHIRE-I[23,24]	International, randomised, double-blind, placebo-controlled Phase III trial	AbbVie 3D + RBV	12 weeks	631
			GT1	C-WORTHy[36]	Randomised Phase IIb trial	MK-5172 + MK-8742 +/- RBV	12 weeks	159
		HIV co-infected	GT1	ERADICATE[16]	Nonrandomised Phase II trial	LDV/SOF	12 weeks	50
	Treatment-experienced		GT1	SAPPHIRE-II[25,26]	International, randomised, double-blind, placebo-controlled Phase III trial	AbbVie 3D + RBV	12 weeks	394
Cirrhotic or non-cirrhotic patients	Treatment-naïve		GT1	ION-1[1,2]	Randomised, open-label Phase III trial	LDV/SOF +/- RBV	12 vs 24 weeks	865
			GT4	PEARL-I[34]	International, nonrandomised, open-label Phase IIb study	AbbVie 2D +/- RBV	12 weeks	135
	Treatment-naïve or treatment-experienced	Treatment-naïve /null or partial responders/ IFN ineligible or intolerant	GT1b	HALLMARK-DUAL[41]	Double-blinded, placebo-controlled, randomised, multicentre Phase III trial	DAC + ASU	24 weeks	745
		Treatment-naïve or previous null responders	GT1	COSMOS cohort II[39]	Multicentre, open-label, randomised Phase IIa study	SIM + SOF +/- RBV	12 vs 24 weeks	87

Table 1 continued.

Patient characteristics	Previous therapy	Subpopulation	HCV GT	Study name/ Reference	Type of study	Investigated compounds	Treatment duration	N
Cirrhotic or non-cirrhotic patients	Treatment-naïve	Cirrhotic	GT1	C-WORTHy[37]	Randomised Phase IIb trial	MK-5172 + MK-8742 +/- RBV	12-18 weeks	253
	Treatment-experienced	Null responders to peg-IFN/RBV						
	Treatment-experienced		GT1	ION-2[5,6]	Randomised, open-label Phase III trial	LDV/SOF +/- RBV	12 vs 24 weeks	440
	Treatment-experienced	Null responders to peg-IFN/RBV	GT1	COSMOS cohort I[38]	Multicentre, open-label, randomised Phase IIa study	SIM + SOF +/- RBV	12 vs 24 weeks	80
	Sofosbuvir-experienced		GT1	ELECTRON-2[13]	Partially randomised, open-label Phase II trial	LDV/SOF +/- RBV	12 weeks	90
	Treatment-naïve		GT3					
		Decompensated cirrhosis (CTP B)	GT1					
		Post-transplant severe recurrence	All	[22]	Compassionate use program	SOF + RBV +/- IFN	48 weeks	104
		Post-transplant recurrence	GT1	M12-999[35]	Single-arm, open-label Phase II study	AbbVie 3D + RBV	24 weeks	34
Cirrhotic patients	Treatment-naïve or treatment-experienced		GT1	TURQUOISE-II[27,28]	Open-label, prospective, randomised Phase III trial	AbbVie 3D + RBV	12 vs 24 weeks	380
		Portal hypertension +/- decompensated liver disease	All	[12]	(Interim results) multicentre, open-label, randomised Phase II trial	SOF + RBV	48 weeks	50

AbbVie 2D: ABT-450/ritonavir/ombitasvir; AbbVie 3D: ABT-450/ritonavir/ombitasvir + dasabuvir; ASU: asunaprevir; CTP: Child-Turcotte-Pugh; DAC: daclastavir; GT: genotype; HCV: hepatitis C virus; peg-IFN: pegylated-interferon; RBV: ribavirin; SIM: simeprevir; SOF: sofosbuvir; LDV: ledipasvir; LDV/SOF: LDV + SOF fixed-dose combination.

Studies in Common Patient Populations

The ION studies

The three open-label, randomised, Phase III ION trials explored the association of 400 mg SOF and 90 mg LDV as a once-daily oral single tablet FDC with or without RBV in 1,952 GT1 patients. GT1 is the most common GT of HCV in the developed world and is less responsive to IFN and RBV than other GTs. Clinical settings comprised treatment-naïve patients (ION-1[1,2]/ION-3[3,4]) and treatment-experienced patients (ION-2[5,6]), with or without cirrhosis, receiving the FDC for 12 or 24 weeks, 8 or 12 weeks, or 12 and 24 weeks, respectively. Across all three studies, therapy arms showed sustained virologic responses (SVR) after 12 weeks post-treatment (SVR12) in 93.1-99.1% of patients, with an overall SVR of 97%. Only 36 patients (1.8%) experienced failures due to virological relapse; 2 further patients had a virological breakthrough and were confirmed to be non-adherent. Although long-term follow-up data will be required to confirm the durability of the response, it is likely that SVR12 data equate to a virological cure. The impact of a virological cure on long-term morbidity and mortality is awaited with interest, but likely to be very positive, as already shown in patients who cleared infection after an IFN-based treatment.

Table 2: Key results from studies presented at the 2014 ILC: sofosbuvir regimens.

Study	Treatment arms	TN/TE	GT	Cirrhosis / Subpopulation	SVR12 (%) or primary endpoint	Virologic failure (%)	AEs (occurrence, %; discontinuations due to AE, %; most common AEs)	
SOFOSBUVIR								
ION-1 (N=865)[1,2]	LDV/SOF, 12 weeks (n=214)	TN	GT1	16% cirrhotic	98.6 (94.1 in cirrhotic pts)	0.5	79.0; 0.0	Fatigue, headache, insomnia most common in all groups
	LDV/SOF + RBV, 12 weeks (n=217)			15% cirrhotic	97.2 **(100 in cirrhotic pts)**	0.0	85.2; 0.0	
	LDV/SOF, 24 weeks (n=217)			15% cirrhotic	97.7 (93.9 in cirrhotic pts)	0.9	82.0; 1.8	
	LDV/SOF + RBV, 24 weeks (n=217)			17% cirrhotic	99.1 **(100 in cirrhotic pts)**	0.0	92.1; 2.7	
ION-2 (N=440)[5,6]	LDV/SOF, 12 weeks (n=109)	TE	GT1	20% cirrhotic	93.6 (86.4 in cirrhotic pts)	6.4	67.0; 0.0	Fatigue, headache, nausea most common in all groups
	(N=440)5,6			20% cirrhotic	96.4 (81.8 in cirrhotic pts)	3.6	86.5; 0.0	
	LDV/SOF, 24 weeks (n=109)			20% cirrhotic	99.1 **(100 in cirrhotic pts)**	0.0	80.7; 0.0	
	LDV/SOF + RBV, 24 weeks (n=111)			20% cirrhotic	99.1 **(100 in cirrhotic pts)**	0.9	90.1; 0.0	
ION-3 (N=647)[3,4]	LDV/SOF, 8 weeks (n=215)	TN	GT1	Non-cirrhotic	94.0	5.1	67.4; 0.0	Fatigue, headache, nausea most common in all groups
	LDV/SOF + RBV, 8 weeks (n=216)				93.1	4.2	76.4; 0.9	
	LDV/SOF, 12 weeks (n=216)				95.4	1.4	69.0; 0.9	
SOF + GS-5816 (N=154)[9]	SOF + GS-5816 25 mg, 12 weeks (n=77)	TN	All	Non-cirrhotic	GT1 96.3; GT2 90.9; GT3 92.6; **GT4 100; GT5 100; GT6 100**	3.9	67.5; 0.0	Fatigue, headache, nausea most common in all groups
	SOF + GS-5816 100 mg, 12 weeks (n=77)				**GT1 100; GT2 100;** GT3 92.6; GT4 85.7; GT5 N/A; **GT6 100**	1.3	70.1; 0.0	
Portal hypertension (N=50, current analysis at 24 weeks)[12]	SOF + RBV, 48 weeks (n=25)	TE 68%	All	Cirrhotic	SVR data were not yet available at the time of presentation. HCV RNA < LLOQ (%): **100** in CTP A pts, 93.3 in CTP B pts	N/A	64.0; 4.0	Nausea, asthenia, pruritus most common in all groups
	Observation, 24 weeks then SOF + RBV for 48 weeks (n=25)	TE 92%			N/A	N/A	56.0; 0.0	
ELECTRON-2 (N=90)[13]	LDV/SOF + RBV, 12 weeks (n=19)	SOF-experienced	GT1	Non-cirrhotic	**100**	N/A	89.5; 0.0	Headache, upper respiratory tract infection, nausea most common in all groups
	LDV/SOF + RBV, 12 weeks (n=26)	TN (n=51)	GT3	19% cirrhotic	**100**	N/A	88.5; 0.0	
	LDV/SOF, 12 weeks (n=25)			12% cirrhotic	64.0	N/A	100; 4.0	
	LDV/SOF, 12 weeks (n=20)		GT1	Decompensated cirrhosis (CTP B)	65.0	N/A	95.0; 0.0	

Table 2 continued.

Study	Treatment arms	TN/TE	GT	Cirrhosis / Subpopulation	SVR12 (%) or primary endpoint	Virologic failure (%)	AEs (occurrence, %; discontinuations due to AE, %; most common AEs)
SOFOSBUVIR							
ERADICATE (N=50), interim results[16]	LDV/SOF, 12 weeks	TN	GT1	Non-cirrhotic, ARV-untreated pts (n=13)	ARV-untreated pts: **100** (SVR4 **100**)	N/A	N/A; fatigue, pain, diarrhoea, constipation most common
				Non-cirrhotic, ARV-treated pts (n=37)	ARV-treated pts: N/A (SVR4 **100**)	N/A	N/A; headache, coryza, nausea, myalgia most common
Post-transplant recurrence (N=104)[22]	Compassionate SOF + RBV, 24 + 48 weeks (n=85)	N/A	All	54% cirrhotic	62.4 (all arms)	N/A	N/A; 48.1% serious AEs in all patients
	Compassionate SOF + RBV + peg-IFN, 24 + 48 weeks (n=22, results not yet available)						

AE: adverse event; ARV: antiretroviral; CTP: Child-Turcotte-Pugh; GT: genotype; LDV: ledipasvir; LLOQ: lower limit of quantification; N/A: not applicable or data not available; peg-IFN: pegylated-interferon; pts: patients; 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. Virologic failure was defined as either breakthrough or virologic relapse; RNA: ribonucleic acid.

The safety profiles of the FDC regimes were excellent, particularly in treatment arms without RBV, indicating that many patients can benefit from sustained high clinical benefits without the burden of RBV or IFN-associated adverse events. Previous pilot studies of treatment duration with all-oral combination regimens indicated that 12 weeks treatment in non-cirrhotic patients was sufficient, and the ION-3 extended the concept of shorter duration treatment by comparing 8 and 12-week regimens. There were no significant differences in the SVR12 rates between both groups without RBV (94.0% and 95.0%, respectively), indicating that the 8-week regimen may be the optimal regimen for non-cirrhotic treatment-naïve patients.[3,4]

The ION-2 study examined challenging patient populations, including 20% of people with cirrhosis, and indicated that the benefits of extending therapy from 12 to 24 weeks were minimal, and not statistically significant (SVR12, 93.6% and 99.1% in RBV-free regimens, respectively, and 96.4% and 99.1% in RBV regimens). There were fewer side-effects but also a slightly higher absolute number of virological relapses in the shorter duration of therapy arms.[5,6] The all-oral combinations were very well tolerated and this was formally assessed in the ION-1 study where patient-reported outcomes indicated that patients from the RBV-free arm benefited from a better quality of life and work productivity, as well as less fatigue than patients receiving RBV-containing combination.[7] Based on these results, it seems that treatment-naïve patients, which are easy to cure, especially in the absence of cirrhosis, might benefit from short therapies (8 weeks), with a single daily tablet regimen of LDV/SOF, whereas treatment-experienced patients may need at least 12 weeks.

SOF + GS-5816 in treatment-naïve patients

SOF was also investigated in combination with GS-5816, an NS5A inhibitor with activity in all GTs as demonstrated by a previous monotherapy study.[8] In this Phase II trial,[9] the SOF + GS-5816 combination was evaluated across all GTs in 154 treatment-

naïve non-cirrhotic patients, who received 400 mg SOF with either 25 or 100 mg GS-5816. 96.3% and 100% of G1 patients from the 25 and 100 mg treatment arms achieved an SVR12, respectively. Similarly, every SVR12 rate for GT2-6 was higher than 90%, while failures occurred in more patients from the 25 mg arm than the 100 mg arm. Most adverse events were low grade and of mild intensity, and overall the treatment was well-tolerated. This combination will be further explored in additional studies in previously-treated patients and in cirrhotic patients.[10,11]

Studies in Specific Populations

SOF was explored in association with RBV in patients with advanced liver disease, including portal hypertension, decompensated cirrhosis, HIV co-infection, or recurrence of HCV following liver transplantation.

Portal hypertension with or without decompensated liver disease

A Phase II trial was initiated to assess the efficacy and safety of SOF in patients with portal hypertension.[12] 50 HCV patients with advanced cirrhosis (including about 60% of Child-Turcotte-Pugh Class [CTP] B patients) and portal hypertension (hepatic venous pressure gradient >6 mmHg) were included in the study, with half receiving combination therapy with 400 mg SOF and RBV for 48 weeks, and half assigned to the observation group (crossing-over to active therapy after 6 months). HCV RNA was undetectable as early as 4 weeks in most patients, with an acceptable safety profile. Compensated cirrhosis was a beneficial factor for on-treatment response to therapy as compared with decompensated cirrhosis (100% and 93.3% in CTP A and B patients, respectively). Inflammation was markedly improved, as ALT levels significantly decreased among all patients in the treatment arm, with clinical improvements noted for ascites and hepatic encephalopathy. Model for end-stage liver disease (MELD) scores were improved from baseline, particularly in CTP B patients; however, some patients had a MELD increase even if they were HCV RNA undetectable.

Decompensated cirrhosis GT1 or SOF-experienced GT1 or treatment-naïve GT3 (ELECTRON-2)

The Phase II ELECTRON-2 study[13] evaluated the efficacy and safety of the once-daily FDC of 400 mg SOF + 90 mg LDV with or without RBV within three patient cohorts: GT1 patients who did not achieve an SVR12 after 12 weeks of a SOF regimen (n=19); GT1 patients with decompensated cirrhosis (n=20); and treatment-naïve GT3 patients (n=51). At 12 weeks, 100% and 65% of patients in the first and second cohorts achieved an SVR12. 64% of treatment-naïve GT3 patients receiving the LDV/SOF FDC achieved an SVR12 compared with 100% in patients from this same cohort receiving additional RBV. The FDC was well-tolerated across the three cohorts.

HIV co-infection (ERADICATE)

HCV-HIV co-infected patients do not seem to respond to IFN-based regimens as well as HCV-only infected patients,[14] but they do appear to benefit from a similar or improved response with IFN-free treatments or DAA regimens containing IFN.[15] The ERADICATE study was initiated to determine whether the FDC of 400 mg SOF + 90 mg LDV[16] was effective in co-infected patients. In 100% of these GT1 HIV co-infected patients, the 12-week regimen yielded undetectable HCV RNA at week 4, 100% of SVR12 for antiretroviral-untreated patients, and 100% of SVR4 in antiretroviral-treated patients. The treatment regimen was well-tolerated overall. Unlike other agents, SOF and LDV have generally very low potential for drug-drug interactions, including with antiretrovirals, which is of importance in this patient population.[17,18]

Severe post-transplant recurrent hepatitis C

Patients undergoing liver transplantation for chronic HCV are invariably re-infected, and a proportion of patients develop very aggressive disease recurrence – often characterised by cholestasis. This patient subpopulation is associated with rapid liver disease progression, liver graft loss, and death within a year.[19-21] Within a compassionate use programme, data analysis allowed a multicentre team to evaluate the efficacy and safety of SOF + RBV in 104 such patients who received the combination for 24-48 weeks.[22] In about one-quarter of the cases, pegylated (peg)-IFN was added to the regimen, as allowed by the study protocol. Among patients who received at least one dose of SOF, the clinical outcomes were improved in 62%, while the disease remained stable in 21%, and worsened or resulted in death in 21%. In patients who completed the study and did not undergo a repeat transplant, the response rate (undetectable HCV RNA) was 87% at end of treatment and SVR12 was 62.4%. These rates are lower than those for the general HCV population but

still represent a life-saving option in this critically ill and difficult-to-treat subpopulation, and are an important proof of principle, showing that antiviral therapy in patients with post-transplant severe recurrent HCV disease can provide resolution of the disease in a majority of cases. Studies with SOF + LDV containing regimens are awaited with great interest.

ABBVIE '2D' AND '3D' COMBINATION REGIMENS

Previous Phase II trials have identified an optimal combination of a ritonavir-boosted protease inhibitor, an NS5A inhibitor, and a non-nucleoside HCV polymerase inhibitor, which, in a regimen together with additional RBV, is highly effective in GT1 patients. AbbVie '2D' is a once-daily combination comprising ABT-450, ritonavir, and ombitasvir (150 mg/100 mg/25 mg), while AbbVie '3D' is the same combination with added 250 mg dasabuvir and RBV in a twice-daily pill, thus comprising five drugs. New clinical data from large cohorts of patients treated with these regimens are presented (Table 3).

Studies in Common Patient Populations

SAPPHIRE I

SAPPHIRE I was a double-blind, placebo-controlled Phase III trial evaluating a combination of ABT-450/ritonavir/ombitasvir + dasabuvir and RBV ('AbbVie 3D') versus placebo in, respectively, 473 and 158 treatment-naïve, non-cirrhotic GT1 patients.[23,24] Patients receiving placebo crossed over to active therapy at week 12. In the active treatment arm, high response rates were observed with an SVR12 of 96.2% in all patients, and of 95.3% and 98.0% in GT1a and GT1b patients, respectively. Virologic failure only occurred in eight patients (1.7%; 7 GT1a, 1 GT1b) and the relapse rate was 1.5%. Therapy was very well tolerated with the most common adverse events in all patients being fatigue and headache; there were significant differences between the placebo and treatment group. Only 0.6% of patients discontinued from the study due to adverse events.

Table 3: Key results from studies presented at the 2014 ILC: AbbVie regimens.

Study	Treatment arms	TN/TE	GT	Cirrhosis / Subpopulation	SVR12 (%) or primary endpoint	Virologic failure (%)	AEs (occurrence, %; discontinuations due to AE, %; most common AEs)	
ABBVIE 3D + RBV								
SAPPHIRE I (N=631)[23,24]	AbbVie 3D + RBV, 12 weeks (n=473)	TN	GT1 (all pts)	Non-cirrhotic	96.2	1.7	Active therapy: 87.5; 0.6; fatigue, headache, nausea most common (no significant difference between the two treatment arms)	
			GT1a		95.3	2.2		
			GT1b		98.0	0.7		
	Placebo (n=158), 12 weeks then AbbVie 3D + RBV until week 24		GT1 (all patients)		(Calculated historical control regimen) 78.0	N/A		
			GT1a		72.0	N/A		
			GT1b		80.0	N/A		
SAPPHIRE II (N=394)[25,26]	AbbVie 3D + RBV, 12 weeks (n=297)	TE	GT1 (all pts)	Non-cirrhotic	96.3	2.3	91.2; 1.0	Headache, fatigue, nausea most common in all groups
			GT1a		96.0	N/A		
			GT1b		96.7	N/A		
	Placebo (n=97), 12 weeks then AbbVie 3D + RBV until week 24		GT1 (all pts)		N/A	N/A	82.5	
			GT1a			N/A		
			GT1b			N/A		

Table 3 continued.

Study	Treatment arms	TN/TE	GT	Cirrhosis / Subpopulation	SVR12 (%) or primary endpoint	Virologic failure (%)	AEs (occurrence, %; discontinuations due to AE, %; most common AEs)	
ABBVIE 3D + RBV								
TURQUOISE II (N=380)[27,28]	AbbVie 3D + RBV, 12 weeks (n=208)	TN 41.3%	GT1	Compensated cirrhosis, all DAA-TN	91.8	6.4	91.8; 1.9	Fatigue, headache, nausea most common in all groups
			GT1a		88.6 (92.2 TN; 93.3 previous relapse; **100 previous partial response;** 80.0 previous null response)			
			GT1b		98.5 (**100 TN; 100 previous relapse;** 85.7 previous partial response; **100 previous null response**)			
	AbbVie 3D + RBV, 24 weeks (n=172)	TN 43.0%	GT1		95.9	2.3	90.7; 0.6	
			GT1a		94.2 (92.9 TN; **100 previous relapse; 100 previous partial response;** 92.9 previous null response)			
			GT1b		**100**			
PEARL I (N=257, interim results on 135 non-cirrhotic pts)[34]	AbbVie 2D (n=44), group 1	TN	GT4	Non-cirrhotic	90.9	6.8	77.3; 0.0	Headache, asthenia, fatigue, nausea most common in all groups
	AbbVie 2D + RBV (n=42), group 4	TN			**100**	0.0	88.1; 0.0	
	AbbVie 2D + RBV (n=49), group 6	TE			N/A	0.0	85.7; 0.0	
M12-999 (post-transplant recurrence, N=34)[35]	AbbVie 3D + RBV	N/A	GT1	N/A	96.2	2.9	97.1; 2.9; Headache, fatigue, cough, insomnia most common	

AbbVie 2D: ABT-450/ritonavir/ombitasvir; AbbVie 3D: ABT-450/ritonavir/ombitasvir + dasabuvir; AE: adverse event; DAA: direct-acting antivirals; GT: genotype; N/A: not applicable or data not available; pts: patients; RBV: ribavirin; SVR12: sustained virologic response 12 weeks after completion of therapy; TE: treatment-experienced; TN: treatment-naïve. Virologic failure was defined as either breakthrough or virologic relapse.

SAPPHIRE II

SAPPHIRE II was a double-blind, placebo-controlled, Phase III trial evaluating ABT-450/ritonavir/ombitasvir + dasabuvir and RBV versus placebo in, respectively, 297 and 97 treatment-experienced, non-cirrhotic GT1 patients.[25,26] Patients receiving placebo crossed over to active therapy at week 12. In the active treatment arm, high response rates were observed with an SVR12 of 96.3% in all patients, and SVRs of 95.3%, 100%, and 95.2% in prior peg-IFN/RBV relapsers, partial-responders, and null responders, respectively. No patient showed a virologic breakthrough, and relapse only occurred in seven patients (2.3%). The most common adverse events in all patients were headache and fatigue. There were significant differences between the placebo and treatment group. Grade 2 anaemia was reported to be <5%.

TURQUOISE II

In an open-label Phase III trial, the 'AbbVie 3D' combination was evaluated in 380 GT1 cirrhotic patients, a challenging population, for 12 or 24 weeks.[27] 58% of patients were peg-IFN and RBV-experienced, while 36% were previous null responders. SVR12 rates were of 91.8% and 95.9% after 12 and 24 weeks of treatment, respectively.[28] SVR12 rates were of 88.6% and 98.5% in G1a and G1b patients in the 12-week arm and 94.2% and 100% in the 24-week arm, respectively. The lowest SVR12 rates were observed with GT1a patients who previously were null responders and who received the combination for 12 weeks (80%). The safety profile was similar to those observed in other clinical trials on the 'AbbVie 3D' five-drug regimen; most adverse events were mild-to-moderate with only 2% of patients discontinuing due to adverse events.

PEARL I

GT4 HCV is the most prevalent GT in the Middle East and its incidence and prevalence is rising in European countries.[29-31] This GT is associated with a relatively low response to peg-IFN or RBV therapy and not all DAAs are active against it.[32,33] Therefore, the Phase IIb PEARL-I study aimed to evaluate the 'AbbVie 2D' combination, with or without RBV for 12 weeks, in GT4 patients who were either non-cirrhotic or had compensated cirrhosis (n=135).[34] Early results, only available in non-cirrhotic patients, revealed that SVR12 was achieved in 90.9% of patients receiving the 'AbbVie 2D' regimen and in 100% of those who received additional RBV. Overall, the treatment was well tolerated and no patients discontinued the study due to adverse events.

Studies in Relapsing Liver Transplant Recipients

M12-999

While HCV is one of the main causes for liver transplantation, almost all patients are re-infected, and about 30% of transplanted patients develop cirrhosis within the first 5 years.[19-21] In this patient subpopulation, the need for a cure is of the utmost importance as these patients suffer from a substantial disease with poor responses to IFN-based regimens. The open-label Phase II M12-999 study[35] aimed to explore the efficacy and safety of the 'AbbVie 3D' regimen + RBV combination in GT1 patients with recurrent HCV infection (n=34) for a treatment duration of 24 weeks. 53% of patients were F0-F1 while 47% were F2. 96.2% of patients achieved an SVR12, while 97% of patients achieved an SVR4. Overall, the combination regimen was well tolerated.

FURTHER HIGHLIGHTED STUDIES

MK-5172/MK-8742 (C-WORTHy)

Two other DAAs, MK-5172 (a second-generation protease inhibitor) and MK-8742 (an NS5A inhibitor), were evaluated as a combination with or without RBV in the two Phase IIb C-WORTHy studies (Table 4). Treatment durations of 8-18 weeks were examined. The first study recruited GT1 patients (n=159) who were treatment-naïve and non-cirrhotic. High response rates were observed with SVR4-24 of 83.3-97.7% across all therapy arms and treatment durations; the highest were observed in the 12-week arms.[36] The second study evaluated this combination in two GT1 cohorts (n=253): treatment-naïve cirrhotic patients and treatment-experienced patients who were null-responders to peg-IFN or RBV. Similarly, high response rates were observed in both populations, with SVR4/8 rates of 90-97% in the treatment-naïve cohort and of 91-100% in previous null responders.[37] In both studies, treatment was well tolerated, with respectively zero and three patients discontinuing due to adverse events, the most commonly reported being fatigue, headache, and asthenia. While these results are certainly promising, interim data need to be further analysed and upcoming SVR12 results will be determinant in assessing the ability of this combination regimen to provide long-term cures

to these patient categories, as well as ongoing Phase III studies.

Simeprevir (COSMOS)

The COSMOS study evaluated simeprevir + SOF with or without RBV for 12-24 weeks (Table 4). This study included two GT1 cohorts: treatment-experienced patients who were null responders to peg-IFN or RBV (n=80);[38] and cirrhotic patients, either treatment-naïve or previous null-responders (n=87).[39] High SVR12 rates were observed in both groups, with 79.2-96.3% of patients achieving this endpoint in the first cohort and 92.6-100% in the second cohort. Addition of RBV did not affect SVR rates, nor did treatment duration. Subgroup analysis revealed two factors associated with lower SVR12 in the first cohort, namely GT1a HCV with Q80K variant present at baseline and IL28B TT GT. The safety profile of the combination was acceptable and only one patient discontinued due to an adverse event unrelated to the study. However, the adverse event rate was higher in the RBV arms. Four patients experienced a serious adverse event during the study. Following these promising results, two Phase III trials (OPTIMIST-1 and 2)[40] are currently ongoing with simeprevir + SOF in GT1 patients.

Daclatasvir/Asunaprevir (HALLMARK-DUAL)

Daclastavir, an NS5A inhibitor currently being investigated in Phase III studies in combination with SOF, was evaluated in the HALLMARK-DUAL Phase III study[41] as an FDC with asunaprevir (an NS3 protease inhibitor active on GT1 and GT4) (Table 4) for 24 weeks. Among the 643 patients recruited in the study, all had HCV GT1b and were either treatment-naïve, null or partial responders, or IFN-ineligible/intolerant. The results showed SVR12 rates ranged from 73% (advanced fibrosis/cirrhosis in IFN ineligible/intolerant patients) to 89.6% (treatment-naïve), while SVR12 in previous null responders and partial responders were both of 82%. Similar rates were observed between cirrhotic and non-cirrhotic patients. Overall, the FDC was well tolerated, with 2% of patients discontinuing the study due to adverse events.

Table 4: Key results from studies presented at the 2014 ILC: MK-5172/MK-8742, simeprevir and daclastavir/asunaprevir/BMS-791325 regimens.

Study	Treatment arms	TN/TE	GT	Cirrhosis / Subpopulation	SVR12 (%) or primary endpoint	Virologic failure (%)	AEs (occurrence, %; discontinuations due to AE, %; most common AEs)	
MK-5172 / MK-8742								
C-WORTHy (N=159)[36]	MK-5172 100 mg + MK-8742 20-50 mg + RBV, 8 weeks (n=30)	TN	GT1	Non-cirrhotic	SVR4-24: 83.3%	16.7	N/A, 0.0; serious AEs: 0.9%	Fatigue, headache, nausea most common in all groups
	MK-5172 100 mg + MK-8742 20-50 mg + RBV, 12 weeks (n=85)				SVR4-24: 94.1%	2.4		
	MK-5172 100 mg + MK-8742 50 mg, 12 weeks (n=44)				SVR4-24: 97.7%	2.3	N/A, 0.0; serious AEs: 0.0%	

Table 4 continued.

Study	Treatment arms	TN/TE	GT	Cirrhosis / Subpopulation	SVR12 (%) or primary endpoint	Virologic failure (%)	AEs (occurrence, %; discontinuations due to AE, %; most common AEs)	
MK-5172 / MK-8742								
C-WORTHy (N=253)[37]	MK-5172 + MK-8742 + RBV (n=63), 12 or 18 weeks	TN	GT1	Cirrhotic	SVR4-8: 90 (12 weeks); SVR4-8: 97 (18 weeks)	MK-5172 + MK-8742 + RBV pts (n=129): 2.3 MK-5172 + MK-8742 pts (n=127): 4.7	N/A, 3.2; serious AEs: 1.6	Fatigue, headache, asthenia most common in all groups
	MK-5172 + MK-8742 (n=60), 12 or 18 weeks	TN		Cirrhotic	SVR4-8: 97 (12 weeks); SVR4-8: 97 (18 weeks)		N/A, 0.0; serious AEs: 3.3	
	MK-5172 + MK-8742 + RBV (n=65), 12 or 18 weeks	TE null responders to peg-IFN/ RBV		38% cirrhotic	SVR4-8: 94 (12 weeks); SVR4-8: **100** (18 weeks)		N/A, 1.6; serious AEs: 3.2	
	MK-5172 + MK-8742 (n=65), 12 or 18 weeks	TE null responders to peg-IFN/ RBV		40% cirrhotic	SVR4-8: 91 (12 weeks); SVR4-8: 97 (18 weeks)		N/A, 0.0; serious AEs: 3.3	
SIMEPREVIR								
COSMOS Cohort I (N=80)[38]	SIM + SOF + RBV, 24 weeks (n=24)	TE null responders to peg-IFN/ RBV	GT1	Cirrhotic and non-cirrhotic	79.2	16.7	N/A	
	SIM + SOF, 24 weeks (n=15)				93.3	6.7	N/A	
	SIM + SOF + RBV, 12 weeks (n=27)				96.3	0.0	N/A	
	SIM + SOF, 12 weeks (n=14)				92.9	0.0	N/A	
COSMOS Cohort II (N=87)[39]	SIM + SOF + RBV, 24 weeks (n=30)	TN or TE null responders to peg-IFN/ RBV	GT1	43% cirrhotic	93.3	0.0	N/A, 0.0. serious AEs: 10.0%;	Fatigue, headache, nausea most common in all groups

Table 4 continued.

Study	Treatment arms	TN/TE	GT	Cirrhosis / Subpopulation	SVR12 (%) or primary endpoint	Virologic failure (%)	AEs (occurrence, %; discontinuations due to AE, %; most common AEs)	
SIMEPREVIR								
COSMOS Cohort II (N=87)[39]	SIM + SOF, 24 weeks (n=16)	TN or TE null responders to peg-IFN/ RBV	GT1	63% cirrhotic	**100**	0.0	N/A, 6.3; serious AEs: 6.3%	Fatigue, headache, nausea most common in all groups
	SIM + SOF + RBV, 12 weeks (n=27)			41% cirrhotic	92.6	7.4	N/A, 0.0; serious AEs: 0.0%	
	SIM + SOF, 12 weeks (n=14)			50% cirrhotic	92.9	7.1	N/A, 0.0; serious AEs: 0.0%	
DACLASTAVIR / ASUNAPREVIR								
HALLMARK-DUAL (N=745)[41]	DAC + ASU, 24 weeks (n=203)	TN	GT1b	16% cirrhotic	89.6	6.9	N/A, 3.0; serious AEs: 6.0%	Headache, fatigue, diarrhoea most common in all groups
	Placebo, 12 weeks (n=102)	TN		16% cirrhotic	N/A	N/A	N/A	
	DAC + ASU, 24 weeks (n=205)	Previous null or partial responders		31% cirrhotic	82.4 (null responders); 91.0 (partial responders)	16.1	N/A, 1.0; serious AEs: 5.0%	
	DAC + ASU, 24 weeks (n=235)	IFN ineligible/ intolerant		47% cirrhotic	81.7	13.6	N/A, 1.0; serious AEs: 7.0%	

AE: adverse event; GT: genotype; IFN: interferon; N/A: not applicable or data not available; peg-IFN: pegylated-interferon; RBV: ribavirin; SIM: simeprevir; SOF: sofosbuvir; SVR4-8: sustained virologic response 4-8 weeks after completion of therapy; SVR4-24: sustained virologic response 4 to 24 weeks after completion of therapy; SVR12: sustained virologic response 12 weeks after completion of therapy; TE: treatment-experienced; TN: treatment-naïve. Virologic failure was defined as either breakthrough or virologic relapse; DAC: daclastavir; ASU: asunaprevir.

CONCLUSIONS

The main objective of chronic hepatitis C management is to provide high cure rates with acceptable toxicity. The new era of DAAs has transformed the standard of care, and the 2014 ILC presented the pivotal Phase III trials from the leading combination trials. Response rates were impressive with nearly all treated patients responding to all-oral combination therapy and even some of the most challenging subgroups – post liver transplant recurrent disease and HIV co-infected patients – responded to treatment. The new data will allow clinicians to select the most appropriate, cost-effective regimen for their patients and we look forward to the licensing of these valuable new therapeutics.

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