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REVIEW

Concise review: Interferon-free treatment of hepatitis C virus-associated cirrhosis and liver graft infection

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Abstract

Chronic hepatitis C is a major reason for development of cirrhosis and hepatocellular carcinoma and a leading cause for liver transplantation. The development of direct-acting antiviral agents lead to (pegylated) interferon-alfa free antiviral therapy regimens with a remarkable increase in sustained virologic response (SVR) rates and opened therapeutic options for patients with advanced cirrhosis and liver graft recipients. This concise review gives an overview about most current prospective trials and cohort analyses for treatment of patients with liver cirrhosis and liver graft recipients. In patients with compensated cirrhosis Child-Pugh-Turcotte (CTP) class A, all approved agents are safe and SVR rates do not significantly differ from patients without cirrhosis in general. In patients with decompensated cirrhosis CTP class B or C, daclastasvir, ledipasvir, velpatasvir, and sofosbuvir are approved, and SVR rates higher than 90% can be achieved. Especially for patients with a model of end stage liver disease score higher than 15 and therefore eligible for liver transplantation, data is scarce. Reported SVR rates in patients with cirrhosis CTP class C are lower compared to patients with a less severe liver disease. In liver transplant recipients with a maximum of CTP class A, SVR rates are comparable to patients without LT. Patients with decompensated graft cirrhosis should be treated on an individual basis.

Key words: Hepatitis C; Cirrhosis; Liver transplantation; Direct antiviral agents; Interferon-free antiviral treatment

Core tip: Chronic hepatitis C is a major reason for development of cirrhosis and a leading cause for liver

transplantation. The development of direct-acting antiviral agents (DAA) offered new therapeutic options for patients with advanced cirrhosis and liver graft recipients. This review gives a high topical summary of most current therapeutic options of DAA-based antiviral therapy in patients with hepatitis C virus associated cirrhosis before and after liver transplantation.

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INTRODUCTION

The World Health Organization estimates that approximately 150 million people worldwide are currently infected with the hepatitis C virus (HCV)[1]. Chronic hepatitis C is a major reason for development of cirrhosis and hepatocellular carcinoma (HCC) in Eastern Asia, Europe, and North America and a leading cause for liver transplantation (LT)[2-4]. In patients with HCV associated cirrhosis, the annual incidence of HCC ranges from 1% to 7%[5-7].

Sustained virologic response to antiviral therapy, defined as undetectable HCV-RNA 12 wk (SVR_{12}) after end of treatment (EOT), is associated with improved survival and reduced risk of HCC development in patients without and with cirrhosis[3,8,9]. The former standard treatment for HCV infection based on the combination of (pegylated) interferon-alfa [(peg)-IFN] and ribavirin (RBV) for 12 to 72 wk was associated with limited SVR rates and burdened by therapy associated adverse events[10,11]. In patients with HCV associated cirrhosis registered for liver transplantation (LT), SVR rates after (peg)-IFN ± RBV range between 0% and 50%, depending inter alia on HCV genotype and severity of liver disease[12]. In patients with decompensated cirrhosis, (peg)-IFN based antiviral therapy is contraindicated[12]. In liver transplant recipients, SVR rates to (peg)-IFN based antiviral therapy are low, and interferon-alfa-associated, immune-mediated graft dysfunction is a major concern[12,13].

The development of direct-acting antiviral agents (DAA) for (peg)-IFN free antiviral therapy regimens lead to a remarkable increase in SVR rates and opened therapeutic options for patients with contraindications or low SVR rates to (peg)-IFN based antiviral therapy regimens[14,15]. Currently available DAA can be classified according to the viral target protein as NS3/4A protease inhibitors (PI), NS5B polymerase inhibitors (including non-nucleoside and nucleoside inhibitors) and NS5A-inhibitors[16]. Antiviral regimens containing elbasvir (EBR)/grazoprevir (GZR), simeprevir (SMV), and ombitasvir (OMV)/paritaprevir/r (PTV/r) - with or without dasabuvir (DSV) - are approved by the European Medicine Agency (EMA) and/or the Federal Drug Administration (FDA) with or without RBV for treatment of patients without and with cirrhosis maximum Child-Pugh-Turcotte (CPT) class A. Regimens containing daclatasvir (DCV), ledipasvir (LDV), velpatasvir, and sofosbuvir (SOF) are approved with or without ribavirin (RBV) for patients with all stages of liver disease including cirrhosis CPT class B and C (Table 1). As SOF is not approved for patients with severe renal impairment, there is still no interferon-free therapy regimen approved for patients with decompensated cirrhosis and severe kidney disease. This article gives a concise review on current data of DAA-based antiviral therapy in patients with advanced HCV associated liver disease.

SYSTEMATICAL LITERATURE DATABASE RESEARCH

A PubMed database research using the terms "hepatitis C", "cirrhosis" and "direct acting antiviral" was performed by the date of 21th of February 2016 to identify relevant clinical studies as well as national and international guidelines. The systematic research resulted in 226 hits, from those we identified 16 original articles, 10 case reports/case series, 137 reviews, 3 national guidelines, 8 articles presenting data from DAA trials without participation of cirrhotic patients, and 51 articles investigating other topics than DAA therapy. One article was listed twice. The PubMed research was amended by studies not fully published but known to the authors, and references listed in systematically identified articles. Totally, 27 trials were identified, which reported safety and efficacy of DAA-based antiviral therapy in patients with compensated and decompensated cirrhosis (Table 2)[17-40].

Additionally, a second PubMed database research using the terms "hepatitis C", "liver transplantation" and "direct acting antiviral" was performed to identify relevant clinical studies as well as national and international guidelines dealing with patients in the liver transplant setting. This systematic PubMed research revealed 72 publications, from those we identified 2 original articles, 3 case reports/series, 45 reviews, one national guideline and 21 articles investigating other topics than DAA therapy or animal model studies. The PubMed research was amended by studies not fully published but known to the authors, and references listed in systematically identified articles. In total, 6 trials were identified including also studies known to the authors as congress proceedings and not yet fully published.

DAA-BASED ANTIVIRAL THERAPY IN HCV-ASSOCIATED CIRRHOSIS

The majority of prospective phase Ⅱ and Ⅲ trials

Table 1 Currently approved[1] direct-acting antivirals combination regimens for hepatitis C virus associated cirrhosis

Drug class	Name	Combination DAA partner	Genotype	Ribavirin	Therapy duration (wk)	Approved cirrhosis class (CPT)
NS3/4A protease inhibitors	Simeprevir	Sofosbuvir	1, 4	No	12	A
	Paritaprevir	In fixed combination with ritonavir and ombitasvir	1, 4	No/Yes	12-24	A
	Grazoprevir	In fixed combination with elbasvir	1, 4	No/Yes	12-16	A
NS5A inhibitors	Daclatasvir	Sofosbuvir	1, 3, 4	No/Yes	12-24	A, B, C
	Ledipasvir	In fixed combination with sofosbuvir	1, 3, 4, 5, 6	No/Yes	12-24	A, B, C[2]
	Ombitasvir	In fixed combination with paritaprevir and ritonavir	1, 4	No/Yes	12-24	A
	Elbasvir	In fixed combination with grazoprevir	1, 4	No/Yes	12-16	A
	Velpatasvir	In fixed combination with sofosbuvir	1, 2, 3, 4, 5, 6	No/Yes	12	A, B, C
NS5B non-nucleoside analog polymerase inhibitors	Dasabuvir	Ombitasvir/paritaprevir/ritonavir	1	No/Yes	12-24	A
NS5B nucleoside analog polymerase inhibitors	Sofosbuvir	Daclatasvir Simeprevir Ledipasvir in fixed combination Velpatasvir in fixed combination	1, 2, 3, 4, 5, 6[3]	No/Yes	12-24	A, B, C

[1]Approved by EMA and/or FDA by October 2016. Approval details may differ with respect to region, genotype, and combination partner; [2]Genotype 3, only CPT A; [3]Different approvals for SOF/RBV, and SOF/LDV. Adapted from[96]. CPT: Child-Pugh-Turcotte; DAA: Direct-acting antivirals; EMA: European Medicines Agency; FDA: Food and Drug Administration; LDV: Ledipasvir; RBV: Ribavirin; SOF: Sofosbuvir.

included only a limited number of patients with cirrhosis[17,22,24-26,28,29,32-34,37-40], and only few trials investigated especially patients with (decompensated) cirrhosis[18-20,23,27,30,31,35]. Data of patient subgroups with cirrhosis were not reported discretely in the majority of studies, including, but not focusing on cirrhotic patients. Additionally to prospective, controlled trials, safety and efficacy of DAA regimens were recorded in "real life" cohort studies and compassionate use or early access programs[41-51]. Data obtained from early access and compassionate use programs must be interpreted with caution, because treatment duration and regimens, *e.g.,* use of RBV, are mostly not controlled by respective protocols. Nevertheless, patients with decompensated cirrhosis or high MELD score ($\geqslant$ 16) were enrolled in a substantial number in these trials, and therefore, these data are of interest and will be presented in the respective sections of this review.

APPROVED DAA-BASED TREATMENTS IN PATIENTS WITH COMPENSATED CIRRHOSIS

All currently approved agents can be administered safely in patients with CPT class A cirrhosis in interferon-free antiviral regimens[18,31,35,52-60]. However, with respect to genotype and DAA regimen, some details have to be considered.

Genotype 1

The combination of LDV/SOF with and without RBV was prospectively evaluated in patients with compensated cirrhosis in the ELECTRON (NCT01260350), ELECTRON-2 (NCT01826981), LONESTAR (NCT01329978), ION-1 (NCT01701401), ION-2 (NCT01768286), GS-334-0113 (NCT01975675), and SIRIUS (NCT01965535) trials. The SIRIUS multicentre, double-blinded phase Ⅱ study evaluated LDV/SOF with RBV for 12 in comparison to LDV/SOF without RBV for 24 wk in 155 GT 1 treatment experienced patients with compensated cirrhosis[18]. Median MELD score was 7 in each study arm (range 6-16 for both arms). Overall, SVR_{12} rates were 96% in patients treated with LDV/SOF with RBV for 12 wk, and 97% in patients treated with LDV/SOF without RBV for 24 wk. Adverse events were mild, namely asthenia, headache, pruritus and fatigue being the most common. To overcome the problem, that each of the respective approval trials for LDV and SOF included only a limited number of patients with cirrhosis, an integrated safety and efficacy analysis of these patients across the mentioned studies was performed[42,61]. In a meta-analysis of pooled data from the ELECTRON (NCT01260350), ELECTRON-2 (NCT01826981), LONESTAR (NCT01329978), ION-1 (NCT01701401), ION-2 (NCT01768286), GS-334-0113 (NCT01975675), and SIRIUS (NCT01965535) studies, 513 patients treated with LDV/SOF with and without RBV for 12 or 24 wk were included. The overall SVR_{12} rate was 96%, and SVR was not associated with prior treatment (47% had previously received a protease-inhibitor-containing regimen), treatment duration or use of RBV. Nevertheless, previously treated patients receiving 12 wk of treatment with LDV and SOF without RBV achieved SVR_{12} in only 90%. Of note, no significant safety issue was observed[42]. In conclusion, 12 wk of LDV/SOF without RBV are considered sufficient for treatment-naive patients with compensated cirrhosis and genotype 1 infection, while the addition of RBV is recommended in treatment-experienced patients with liver cirrhosis[62,63].

The combination of SMV and SOF was evaluated in the OPTIMIST-2 phase Ⅲ, open-label, single-arm

Table 2 Efficacy of direct-acting antivirals based, (peg)-interferon-free antiviral therapy in patients with hepatitis C virus-associated (de-) compensated cirrhosis in controlled, prospective trials

Ref.	Therapy regimen	Treatment duration (wk)	Genotype	*n* (all)	*n* (cirrhotic patients)	*n* (MELD > 16)	SVR_{12} % (all patients)
Abergel *et al*[17]	LDV/SOF	12	5	41	9	Not specified	39/41 (95%)
Afdhal *et al*[53] (ION-1)	LDV/SOF ± RBV	12-24	1	865	136	Not specified	849/865 (98%)
Afdhal *et al*[54] (ION-2)	LDV/SOF ± RBV	12-24	1	440	88	Not specified	427/440 (97%)
Bouliere *et al*[18] (SIRIUS)	LDV/SOF ± RBV	12-24	1	155	155	Not specified	149/154 (97%)
Charlton *et al*[19] (SOLAR-1)	LDV/SOF/RBV	12-24	1, 4	337	108	27	89/108 (82%)[1]
Curry *et al*[20] (ASTRAL-4)	VEL/SOF ± RBV	12-24	1, 2, 3, 4, 6	267	267	13	234/267 (88%)
Curry *et al*[21]	SOF/RBV	Up to 48	1, 2, 3, 4	61	61	None	30/43 (70%)
Feld *et al*[22] (ASTRAL-1)	VEL/SOF	12	1, 2, 4, 5, 6	741[2]	142	Not specified	618/624 (99%)[3]
Feld *et al*[23] (TURQUOISE-Ⅲ)	OBV/PTV/r + DSV	12	1b	60	60	Not specified	60/60 (100%)
Forns *et al*[24] (C-SALVAGE)	Grazoprevir/Elbasvir/RBV	12	1	79	34	Not specified	76/79 (96%)
Foster *et al*[25] (ASTRAL-2/-3)	VEL/SOF *vs* SOF/RBV	12	2, 3	818	201	Not specified	742/818 (91%)
Foster *et al*[68] (BOSON)	SOF/RBV ± IFN	12-24	2, 3	592	219	Not specified	494/592 (83%)
Kumada *et al*[26] (GIFT-1)	OBV/PTV/r	12	1b	363	42	Not specified	346/363 (95%)
Lawitz *et al*[27] (OPTIMIST-2)	SMV/SOF	12	1	103	103	Not specified	86/103 (83%)
Lawitz *et al*[28] (C-WORTHY)	Grazoprevir/Elbasvir ± RBV	12-18	1	253	170	Not specified	240/253 (95%)
Lawitz *et al*[29] (PEARL-I)	OBV/PTV/r + DSV	12-24	1	181	99	Not specified	172/181 (95%)
Leroy *et al*[30] (ALLY-3+)	DCV/SOF/RBV	12-16	3	50	50	Not specified	45/50 (90%)
Manns *et al*[31] (SOLAR-2)	LDV/SOF/RBV	12	1, 4	328	160[4]	41	121/140 (86%)
Mizokami *et al*[32]	LDV/SOF ± RBV	12	1	341	76	Not specified	338/341 (99%)
Nelson *et al*[33] (ALLY-3)	DCV/SOF	12	3	152	32	Not specified	135/152 (89%)
Omata *et al*[34]	SOF/RBV	12	2	153	17	Not specified	148/153 (97%)
Poordad *et al*[35] (TURQUOISE-Ⅱ)	OBV/PTV/r + DSV/RBV	12-24	1	380	380	Not specified[5]	356/380 (94%)
Poordad *et al*[36] (ALLY-1)	DCV/SOF/RBV	12	1, 2, 3, 4, 6	113[6]	60	Not specified (CPT C 16)	100/113 (89%)[7]
Poordad *et al*[37] (QUARTZ-I)	OBV/PTV/r + DSV + SOF + RBV	12-24	1	22	7	Not specified	14/15 (93%)[8]
Wyles *et al*[38]	LDV/SOF/RBV	12	1	51	14	Not specified	50/51 (98%)
Zeuzem *et al*[39] (VALENCE)	SOF/RBV	12-24	2, 3	419	90	Not specified	302/334 (90%)[9]
Zeuzem *et al*[40] (C-EDGE)	Grazoprevir/elbasvir	12	1, 4, 6	421	92	Not specified	299/316 (95%)[10]

[1]Only pretransplant cohort; [2]116 patients received placebo; [3]SVR in patients with compensated cirrhosis 99%; [4]Patients with CPT class B or C cirrhosis pre- and posttranplant, additionally CPT class A patients posttransplant participated in this trial, the number was not specified; [5]Only patients with CPT class A cirrhosis included; [6]Only patients who had undetectable HCV-RNA at transplant were included in efficacy analysis; [7]83% in the advanced cirrhosis cohort; [8]Not all patients completed follow up until conference; [9]85 patients received placebo; [10]105 patients had deferred therapy. CPT: Child-Pugh-Turcotte; DAA: Direct-acting antivirals; DCV: Daclatasvir; DSV: Dasabuvir; LDV: Ledipasvir; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir; PTV/r: Paritaprevir/ritonavir; VEL: Velpatasvir; SVR_{12}: Sustained virologic response 12 wk after end of treatment.

study, including 103 GT 1 patients with cirrhosis[27]. The overall SVR_{12} rate was 83%, in detail, 88% and 79% for treatment-naive and treatment-experienced patients, respectively. In patients with baseline albumin levels higher than 40 g/L, SVR_{12} rates were higher than in patients with albumin levels lower than 40 g/L (94% versus 74%).

The combination of OBV/PTV/r and DSV (3D-regimen) was evaluated in two studies in patients with compensated cirrhosis. The TURQUOISE-Ⅱ trial, an open-label phase Ⅲ trial investigated the 3D-regimen in combination with RBV for 12 wk *vs* 24 wk in 380 patients with HCV associated cirrhosis CPT class A[35]. The overall SVR_{12} rate was 93.7%, 91.8% (191/208) in the 12 wk compared to 95.9% (165/172) in the 24 wk group, respectively. A significant reduction of the relapse rate in the longer treatment arm was only observed in patients with HCV subtype 1a infection and one or more specific negative predictors (alfa-fetoprotein > 20 ng/mL, platelet count < 90 × 10^9/L, albumin level < 35 g/L). Negative predictors of SVR in general were IL28B T/T polymorphism, prior null-response to (peg)-IFN/RBV therapy, and genotype 1a infection[35]. The TURQUOISE-Ⅲ phase Ⅲb, open-label study investigated whether RBV could be dispensed without SVR decline in 60 patients with HCV genotype 1b associated cirrhosis treated with the 3D-regimen[23]. Nineteen (32%) patients had clinical signs of portal hypertension (thrombocytopenia, esophageal varices) alone or in combination with reduced serum albumin levels or hepatic coagulopathia. However, all patients included had a CPT score not higher than 6 with no

evidence of hepatic decompensation. Treatment with the 3D-regimen without RBV was safe and efficacious in patients with compensated cirrhosis and genotype 1b infection, as SVR_{12} was achieved in 100%.

The combination of DCV und SOF was evaluated in the ALLY-1 trial, which included patients with compensated and decompensated cirrhosis[36]. Respective results are discussed below.

The therapeutic spectrum for patients with genotype 1 (and 4 or 6) infection was currently widened with the FDA approval of EZR in fixed combination with GZR[64]. A treatment course of 12 wk in patients with mainly genotype 1 infection resulted in an overall SVR_{12} rate of 95% (299/316)[40]. The study included 92 (22%) patients with compensated cirrhosis, and SVR_{12} rates did not differ between treatment naïve patients without or with cirrhosis. Severe adverse events occurred in 9 (2.8%) patients receiving the investigational drugs and 3 (2.9%) patients of the placebo group, but no event was considered drug related[40]. However, HCV subtype (1a *vs* 1b), resistant associated variants, and prior treatment status has to be taken into account according to the FDA approved label of these fixed-combination therapy.

Genotype 2

The currently approved DAA regimens were investigated in a moderate number of patients with cirrhosis and genotype 2 infection[34,39,46,65-67]. According to the European Association for the Study of the Liver (EASL) guidelines, patients with GT 2 and cirrhosis should be treated with SOF/RBV for a prolonged treatment duration of 16 to 20 wk, especially in patients with treatment experience[62].

Genotype 3

Studies investigating DAA based antiviral therapy in patients with HCV genotype 3 associated cirrhosis have shown lower SVR rates than in genotype 1 infected patients for SOF/RBV for 12 to 24 wk and DCV/SOF for 12 wk[33,39]. The ALLY-3+ trial investigated whether the addition of RBV to DCV/SOF and a prolongation of treatment duration from 12 to 16 wk were associated with enhanced SVR rates in 50 GT 3 patients with advanced fibrosis (14/50, 28%) or cirrhosis (36/50, 72%)[30]. The overall SVR_{12} rate was 90%. The SVR rates did not differ significantly between both groups, with 88% (91% observed, excluding a patients who died due to causes not related to study) in the 12 wk group and 92% in the 16 wk group. The subgroup analysis of patients with cirrhosis reported an overall SVR_{12} rate of 86%, with 83% (88% observed) in the 12 wk group compared to 89% in the 16 wk group. Cirrhosis stage or MELD score were not specified. Of note, DCV is approved in combination with SOF and RBV for 12 (FDA) or 24 (EMA) wk in patients with cirrhosis and genotype 3 infection.

The large BOSON trial investigated SOF/RBV for 16 or 24 wk *vs* SOF/RBV ± peg-IFN for 12 wk in treatment-experienced patients with cirrhosis and genotype 2 infection and patients with genotype 3 infection of any treatment status with and without cirrhosis[68]. In HCV genotype 2 infection, the SVR rate was not significantly different in the three treatment arms (87%, 100%, and 94%). In patients with genotype 3 infection, SOF/RBV ± peg-IFN was superior to 16 or 24 wk of SOF/RBV (93% *vs* 71%, 84%). The same pattern with lowest SVR_{12} rate in the 16 wk group was found in the subgroup of patients with genotype 3 infection and cirrhosis.

Genotype 4-6

Patients with HCV genotype 4, 5, or 6 infection and compensated cirrhosis were included in limited numbers only in the respective trials. Current guidelines recommend LDV/SOF with RBV for 12 wk, LDV/SOF without RBV for 24 wk or DCV/SOF with RBV for 12 and without RBV for 24 wk. Of note, DCV/SOF with or without RBV is not approved by EMA for HCV genotype 5 or 6 infection. Additional options for patients with genotype 4 infection are the combination of SMV/SOF with RBV for 12 and without RBV for 24 wk or OBV/PTV/r for 24 wk with RBV[62].

Pan-genotype treatment (genotype 1-6)

The combination of VEL and SOF has been evaluated for 12 wk in phase Ⅲ studies including patients with compensated cirrhosis[22,25]. Among all genotypes, the overall SVR_{12} rates ranged from 95% to 99%. A subgroup analysis was performed for patients with genotype 3 infection, and SVR_{12} did not significantly differ in patients with our without cirrhosis[25]. The fixed drug combination was approved by the EMA and the FDA in 2016 for patients with compensated cirrhosis for a 12-wk treatment without RBV. Addition of RBV may be considered for patients in compensated cirrhosis and genotype 3 infection (EMA).

APPROVED DAA-BASED TREATMENT IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

Randomized, prospective trials of approved DAA regimens were performed in patients with advanced liver disease [(decompensated) cirrhosis, after LT] and mainly HCV genotype 1, 3, and 4 infection. Although some studies investigated patients with "decompensated" cirrhosis, data are scarce in patients with a MELD score higher than 15[69]. From the limited data may be concluded that patients with CPT class C cirrhosis have lower SVR_{12} rates than patients without or with compensated cirrhosis. Improvements of MELD score as well as albumin levels indicate an improvement in liver function in patients with DAA induced SVR[31,70]. However, liver function stayed

unchanged in a significant proportion of patients or even worsened despite of SVR. Moreover, serious adverse events including fatal courses have been reported in patients with decompensated cirrhosis and DAA based antiviral therapy ranging from 18% to 34%[19,20]. Most trials did not report a benefit in SVR rates for 24 wk of treatment over 12-wk duration[18,22]. However, some data indicate similar SVR_{12} rates for a treatment of 12 or 24 wk only with additional RBV in the 12 wk arm[20]. The relevant studies are discussed in detail below.

The randomized open-label phase Ⅱ studies SOLAR-1 and SOLAR-2 evaluated the combined treatment with LDV/SOF and RBV for 12 or 24 wk in patients with HCV GT 1 or 4 and advanced cirrhosis or post liver transplantation[19,31]. Totally 337 patients were enrolled in the SOLAR-1 study, 89% GT 1 and 11% GT 4. Data of 108 patients with decompensated cirrhosis have been reported supplementary prior to the final publication[19,70]. Patients had CPT class B (n = 55) or C (n = 53) cirrhosis, and 26% of patients (28) had a MELD score > 15. At therapy baseline, 96% of patients with cirrhosis CPT class C had ascites. The overall SVR_{12} rate was 87%, and did not differ significantly in patients with CPT class B cirrhosis between the 12 wk (SVR, 87%) and the 24 wk (89%) duration arm. In patients with cirrhosis CPT class C, SVR_{12} rates were 86% and 87% in the respective study arms. Of note, 4 patients with cirrhosis CPT class B/C received a liver graft, 5 patients discontinued treatment because of adverse events, and one patient died. The transplant cohorts of the SOLAR-1 study and the SOLAR-2 study are discussed in the respective section below.

The combination of DCV/SOF and RBV for 12 wk was evaluated in the open label, phase Ⅲ ALLY-1 study in patients with advanced cirrhosis or after LT[36]. Although all genotypes were allowed, mainly patients with genotype 1 infection were included in the cirrhosis cohort (45/60, 75%). Patients transplanted during treatment were eligible for additional 12 wk of treatment immediately post-transplant. In the cirrhosis cohort, CPT class distribution was 20% class A, 53% class B, and 27% class C, and MELD score ranged between 8 and 27. The overall SVR_{12} rate in the cirrhosis cohort was 83% (50/60 patients with all GT) and did not differ with respect to prior treatment status or general baseline characteristics. However, SVR rates were higher in patients with CPT class A (10/11 GT 1 patients) or B (22/24 GT 1 patients) than in patients with class C (5/10 GT 1 patients, for other GT not separately displayed).

The combination of VEL/SOF has also been evaluated in 267 patients with decompensated cirrhosis in the phase Ⅲ, open-label ASTRAL-4 study[20]. Although designed as a pan-genotype study, mainly patients with genotype 1 (78%) and 3 (15%) infection were enrolled, while patients with genotypes 2, 4, 5, and 6 were included only to a low percentage of 4%, 3%, 0%, and < 1%, respectively. Patients were randomized to 12 wk of SOF/VEL with or without RBV or 24 wk with SOF/VEL without RBV. Enrolled patients had a median baseline CPT score of 8 (range 5 to 10) and a median baseline MELD score of 10 (range 6 to 24). However, 95% of patients had a baseline MELD score of 15 or less. At screening all patients had CPT class B, but 7% of patients had CPT class A at treatment baseline. This has to be kept in mind, when transferring scientific data to clinical practice in patients with "truly" decompensated cirrhosis. Overall SVR_{12} rates were 83% for 12 wk of SOF/VEL, 94% for 12 wk of SOF/VEL/RBV and 86% for 24 wk of SOF/VEL. SVR_{12} rates for CPT class or subgroups were not reported separately. An improvement in CPT class was achieved in 47% of patients, 42% had no change and 11% patients showed a worsened CPT score. Overall improvement of MELD score was observed. This effect was stronger in patients with an initial MELD score > 15. In detail, 51% of patients with a baseline MELD score ⩽ 15 showed an improvement of MELD score, while MELD score stayed unchanged or worsened in 22% and 27% of patients, respectively. Patients with a baseline MELD > 15 showed an improved MELD score in 81%, while MELD score stayed unchanged or worsened in 11% and 7%, respectively. Although these are encouraging data, it has to be considered, that (severity of) portal hypertension, a major risk factor of death in patients with cirrhosis, is not adequately reflected by MELD. The fixed combination of VEL/SOF is approved by the EMA and the FDA for 12 wk in combination with RBV.

As mentioned above, data from early access and compassionate use programs, as well as data from "real life" cohorts are useful supplements to prospective controlled trials, because inclusion criteria often allowed to include a substantial number of patients with advanced liver disease, *e.g.,* decompensated cirrhosis. Final data are currently available from the National Health Service England Expanded Access Programme, which included 467 patients with hepatic decompensation or life-threatening extrahepatic manifestations[49]. In this prospective, observational cohort study, patients were treated for a maximum of 12 wk with DCV/SOF ± RBV or LDV/SOF ± RBV by clinician's discretion. The majority (409/467, 88%) of patients had past or current symptoms of hepatic decompensation, defined by presence of ascites, variceal bleeding or encephalopathy. At baseline, 319 patients were classified as CPT class B, and 43 as CPT class C, and median (range) MELD score was 11 (6-32). Overall SVR_{12} was 82% (381/467); 4% (17/467) of patients died and 3% (16/467) of patients were lost to follow-up. In detail, SVR_{12} rates were 85% (39/46) for patients with genotype 1 infection treated with DCV/SOF ± RBV and 92% (170/185) for patients treated with LDV/SOF ± RBV, respectively. Patients with genotype 3 infection achieved SVR_{12} in 73% (91/125) when treated with DCV/SOF ± RBV and in

61% (41/67) treated with LDV/SOF ± RBV[49]. Of note, DCV is currently approved in patients with cirrhosis and HCV genotype 3 infection in combination with SOF and RBV by EMA for 24 wk and by FDA for 12 wk treatment[62,63].

It is unquestionable, that efficacy and safety has improved with DAA based IFN-free therapies compared to (peg)-IFN based therapy regimen in patients with decompensated cirrhosis. For a subgroup of patients with decompensated cirrhosis and DAA induced SVR, an improvement in liver function has been reported. Nevertheless, severe adverse events were reported in a substantial percentage of patients, and ascites or hepatic encephalopathy did not resolve completely in all patients[43,44,49,71]. Currently, no biomarkers are available to predict the individual clinical course in patients with decompensated cirrhosis to decide whether treatment should be initiated before or after LT[49,72].

FURTHER OPTIONS OF DAA-BASED TREATMENT IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

SMV is not approved by the EMA or the FDA for patients with cirrhosis CPT class B or C. Nevertheless, treatment of patients with advanced cirrhosis with SMV/SOF with or without RBV has been reported[43,44]. Saxena *et al*[43] presented data of a multicenter cohort of 106 GT 1 patients with cirrhosis treated with SMV/SOF with or without RBV for 12 wk. Patients were analyzed according to CPT class A versus CPT class B/C and compared to matched untreated controls. The median (range) baseline MELD score in the overall study population was 9 (8-11), and cirrhosis was classified as CPT class A in 64% and CPT class B/C in 35%. Overall, SVR rates were 91% in patients with CPT class A and 73% in patients with CPT class B/C cirrhosis, respectively[43]. Two deaths occurred, one in each group, one liver related and one not. Shiffman *et al*[44] reported retrospectively analyzed data from 120 patients with cirrhosis and HCV genotype 1 infection treated with SMV/SOF. From those 67%, 21% and 12% had CPT class A, B, and C cirrhosis, respectively. Hepatic decompensation or portal hypertension was present in 30% of patients. The overall SVR_{12} rate was 87%, 77%, and 67% in CPT class A, B, and C patients, respectively. Serious adverse events were reported in 11% of patients, sepsis (n = 2, 1/2 fatal outcome), variceal bleeding (n = 2), hepatocellular carcinoma (n = 2), and increase in bilirubin (n = 8). Although these data indicate that SMV might be safe in patients with decompensated cirrhosis, there is general concern because the simeprevir mean steady state area under the curve is increased in patients with CPT class B and C cirrhosis by 2.4-fold and 5.2-fold, respectively (summary of product characteristics).

DAA THERAPY PERI-TRANSPLANT

Curry *et al*[21] conducted an open-label phase Ⅱ study for patients on the waiting list to LT for HCC of any GT. Endpoint of the study was undetectable HCV RNA 12 wk after LT. Patients received SOF and RBV up to 48 wk before LT, 61 patients with CPT ⩽ 7 were included. LT was performed in 46 patients, 43 from those had undetectable HCV RNA at transplant and were included in efficacy analysis. Outcome of those 43 patients was: 30 patients (70%) had SVR12 after LT, 10 patients (23%) suffered from relapse, 3 patients (7%) died (primary graft non-function, n = 2; hepatic artery thrombosis, n = 1). Overall SVR post LT from all 61 patients was 49%. The risk of HCV graft infection was negatively correlated with the time interval before LT, when HCV RNA was undetectable. Safety and efficacy of LDV/SOF are currently investigated in patients with genotype 1 or 4 infection in a peri-transplant setting[73].

ANTIVIRAL THERAPY IN HCV LIVER GRAFT INFECTION

In patients with detectable HCV RNA at transplantation, HCV graft infection is almost inevitable, and HCV infection of the liver graft often shows an aggravated course with development of graft cirrhosis in up to 30% percent of patients within 5 years after transplantation[74,75]. In a minority of patients, HCV graft infection presents as fibrosing cholestatic hepatitis (FCH), a severe form of hepatitis C, leading to graft loss and death within months up to 2 years in the majority of patients[76]. Therefore, HCV graft infection is associated with a decrease in patient and graft survival[77].

Patients with fibrosis or cirrhosis after LT have a poor tolerance and low efficacy to (peg)-IFN based antiviral therapy[78]. Moreover, plasma cell hepatitis is a rare but feared complication of (peg)-IFN therapy[76,79]. First generation PI - in combination with (peg)-IFN and RBV - were associated with a slight increase in SVR rates, but a high rate of serious adverse events[80,81]. The introduction of DAA-based IFN-free antiviral therapy widened therapeutic options in patients after liver transplantation and a proof of concept study using SOF with RBV for 24 wk resulted in an overall SVR rate of 70%[82]. Currently safety and efficacy data of DAA based antiviral therapy in liver graft recipients are available from prospective trials[19,31,36,83,84] and cohort studies[77,85-90]. Table 3 summarizes available prospective and controlled trials. The most important prospective trials are the SOLAR-1 and -2 studies (LDV/SOF/RBV), the CORAL-I study (3D/RBV), and the ALLY-1 trial (DCV/SOF/RBV)[19,31,36,84].

The combination of LDV and SOF with or without RBV was investigated in several studies[19,31,83]. Reddy *et al*[83] performed a prospective, randomized multicenter study to evaluate treatment with LDV/SOF

Table 3 Efficacy of direct-acting antivirals based, (peg-)-interferon-free antiviral therapy in patients with hepatitis C virus liver graft infection in controlled, prospective trials

Ref.	Therapy regime	Treatment duration (wk)	Genotype[1]	*n*	SVR$_{12}$
Charlton *et al*[19] (SOLAR-1)[1]	LDV/RBV + RBV	12-24	1, 4	229[2]	214/229 (93%)
[1]Charlton *et al*[82]	SOF + RBV	24	1, 3, 4	40	28/40 (70%)
Kwo *et al*[84] (CORAL-1)	DSV/OMV/PTV/r + RBV	24	1	34	33/34 (97%)
Manns *et al*[31,72] (SOLAR-2)	LDV/SOF +RBV	12 or 24	1, 4	168[3]	146/151 (97%)
Poordad *et al*[36] (ALLY-1)[1]	DCV/SOF + RBV	12	1, 2, 3, 4, 6[4]	53[2]	50/53 (94%)
Reddy *et al*[83]	SOF/LDV + RBV	12-24	1, 4	223	120/129 (93%)[5]

[1]Mainly patients with genotype 1; [2]The complete study included patients prior and after liver transplantation; [3]Preliminary results with regard to publication status or completed SVR12 (SVR not available in all patients enrolled into the study); [4]Only one patient had GT 2, 4 or 6; [5]Interims SVR4 results. LDV: Ledipasvir; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir; OMV: Ombitasvir; PTV/r: Paritaprevir/ritonavir; SVR12: Sustained virologic response 12 wk after end of treatment.

with RBV for 12 wk *vs* 24 wk in patients with GT1 und GT4 in liver graft recipients at median (range) 4.4 (0.4-23.3) years after LT. Two-hundred-twenty-three patients were enrolled, 83% had prior HCV treatment, 47% of all patients were PI treatment experienced. Fifty percent of patients had F0-F3 fibrosis, while 23%, 22% and 4% had CPT class A, B, and C cirrhosis, respectively. SVR rates were high in patients without (12 wk, 96%; 24 wk, 94%) as well as in patients with graft cirrhosis (12 wk, 92%; 24 wk, 84%). Overall safety was excellent, however, 5 patients with graft cirrhosis died during the study period due to gastrointestinal bleeding, multiorgan failure, intestinal perforation, cardiac problems, complications of cirrhosis and progressive multifocal leukoencephalitis. These early results implicated no difference between 12 and 24 wk of LDV/ SOF plus RBV.

The SOLAR-1 and -2 studies demonstrated high efficacy and an excellent safety profile of LDV/SOF for 12 or 24 wk in patients without and with graft cirrhosis. Both studies have to be highlighted, because cirrhosis stage was well classified, and all stages of severe liver disease after LT namely graft cirrhosis CPT class C and FCH were included. The overall SVR$_{12}$ rates were > 90%. A longer treatment of 24 wk was not superior over 12 wk with respect to SVR in both studies. Nevertheless, lower SVR rates were observed in patients with decompensated graft cirrhosis[19,31].

Thirty-four patients after liver transplantation without and with mild fibrosis (≤ F2) were enrolled in an open label, phase Ⅱ study (CORAL-I) by Kwo *et al*[84] receiving OBV/PTV/r/DSV plus RBV for 24 wk. Patients had a calcineurin inhibitor based immunosuppression. The overall efficacy assessed by SVR$_{12}$ was high with 33/34 (97%). Reported adverse events were mostly mild, fatigue, namely headache, and cough. Of note, substantial dosage modifications of immunosuppressants were required to maintain respective therapeutic levels.

The post-transplant cohort of the ALLY-1 open label, phase Ⅲ study included 53 HCV-infected patients of any genotype to the treatment of 12 wk with DCV/SOF and RBV[36]. Seventy-seven percent of patients had HCV genotype 1 infection. No patients with FCH or decompensated graft cirrhosis were included. The efficacy was high with an overall SVR$_{12}$ rate of 94%. In the compassionate use program of DCV/SOF also patients with FCH or decompensated graft cirrhosis were included, however, the total number (*n* = 12) of respective patients included was low[87]. In this program, patients were treated with DCV/SOF in equal parts with or without RBV for 24 wk. Nine of twelve completed 24 wk of treatment, while three patients died before end of treatment. Preliminary post-treatment data were available for five patients, and so far no viral relapse was reported. Of note, dose adjustment of immunosuppressants was not necessary during treatment.

Robust data for the use of SMV/SOF in liver graft recipients are available from cohort studies, only[77,86,90]. The largest study enrolled 132 patients with HCV genotype 1 infection at median (range) 32 (2-317) months after LT, who were treated with SMF/SOF with and without RBV for 12 wk[86]. Overall, 60% of patients were infected with genotype 1a, 30% had METAVIR F3-F4, 4% had decompensated graft cirrhosis, and 11% had FCH. Furthermore, 7% of patients had also a kidney transplant, and 82% had previously failed (peg)-IFN/RBV-based regimens. Immunosuppression contained tacrolimus in 91%. Overall SVR$_{12}$ rate was 90%. However, patients with genotype 1a infection and advanced fibrosis (METAVIR F3-F4) had significantly lower SVR rates (71%) than those with F0-F2 (91%). Twenty-five patients received RBV (20%) with no significant impact on SVR. However, 72% patients developed clinical relevant anemia. One death - possibly due to drug induced lung injury - occurred, all other adverse events were classified mild. Minimal dose adjustments in immunosuppression were necessary[86]. A further, but smaller study (*n* = 42) is of interest, because 14% of patients with decompensated graft cirrhosis were included. Overall 95% of patients achieved SVR$_{12}$, 97% of patients without and 88% of patients with cirrhosis, respectively (*P* = NS).

DRUG-DRUG INTERACTION BETWEEN DAA'S AND IMMUNOSUPPRESSION

The calcineurin inhibitors ciclosporin and tacrolimus are substrates of CYP3A[91-93]. Clinical significant interactions with ciclosporin and tacrolimus have been described for SMV and OMV/PTV/r. For co-administration of SMV and tacrolimus monitoring of tacrolimus trough blood levels is recommended, while again the co-administration of SMV and ciclosporin is not recommended, because SMV levels may raise (summary of product characteristics). Dose reduction and respective drug monitoring of ciclosporin (20% of daily dose) and tacrolimus (fixed 0.5 mg weekly dose) is recommended for co-administration with OBV/PTV/r ± DSV. Clinical significant drug-drug interactions with DAA have not been reported for mycophenolate mofetil. However, persistent anemia with need of blood cell transfusions was reported due to combined treatment with mycophenolate mofetil and peg-IFN/RBV/SMV[94].

CONCLUSION

There are increasing data reporting DAA based, (peg)-IFN free treatment of patients with HCV associated cirrhosis. In patients with compensated cirrhosis CPT class A, all approved agents are safe and SVR rates do not significantly differ from patients without cirrhosis[95]. In patients with decompensated CPT class B/C cirrhosis, DCV, LDV, VEL and SOF alone or in combination with RBV are safe, and SVR rates > 90% can be achieved. For most patients, a treatment course of 12 wk with or without RBV is considered sufficient. In patients with severest cirrhosis (CPT class C, MELD > 15), data from randomized trials are scarce. However, SVR rates seem lower compared to patients with less severe liver disease, and yet no (bio)markers are available to predict the further clinical outcome.

In patients with HCV graft infection after LT mostly open label trials and cohort analyses, and only few randomized trials are available. Data are conclusive that SVR rates are not different to patients without LT and maximum CPT class A cirrhosis. Patients with decompensated graft cirrhosis should be treated on an individual basis. Moreover, DAA based therapy is relatively safe in patients after LT, and therapy discontinuations due to therapy side effects are rare. Nevertheless, some challenges are to overcome. Potential drug-drug interactions - especially with immunosuppression - and concomitant impaired renal function have to be considered. A cautious surveillance during antiviral therapy is advisable to identify infections and immediately administer antibiotic treatment.

In summary, while all approved agents are eligible for patients with CPT class A cirrhosis, only 4 agents - DCV, LDV, VEL and SOF - are currently approved for patients with all severity of liver disease including CPT class B and C cirrhosis. Liver graft recipients with compensated liver disease can be treated according to patients without prior LT. The standard treatment duration for the majority of patients is 12 wk.

REFERENCES

1 Hepatitis C - Fact sheet N 164. In: Organisation WH, editor. World Health Organization, 2014

2 **Allison RD**, Tong X, Moorman AC, Ly KN, Rupp L, Xu F, Gordon SC, Holmberg SD. Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection, 2006-2010. *J Hepatol* 2015; **63**: 822-828 [PMID: 25937437 DOI: 10.1016/j.jhep.2015.04.021]

3 **van der Meer AJ**, Wedemeyer H, Feld JJ, Dufour JF, Zeuzem S, Hansen BE, Janssen HL. Life expectancy in patients with chronic HCV infection and cirrhosis compared with a general population. *JAMA* 2014; **312**: 1927-1928 [PMID: 25387192 DOI: 10.1001/jama.2014.12627]

4 **Adam R**, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, Castaing D, Neuhaus P, Jamieson N, Salizzoni M, Pollard S, Lerut J, Paul A, Garcia-Valdecasas JC, Rodríguez FS, Burroughs A. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol* 2012; **57**: 675-688 [PMID: 22609307 DOI: 10.1016/j.jhep.2012.04.015]

5 **Degos F**, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, Trinchet JC, Beaugrand M, Chevret S. Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. *Gut* 2000; **47**: 131-136 [PMID: 10861275 DOI: 10.1136/gut.47.1.131]

6 **Fattovich G**. Progression of hepatitis B and C to hepatocellular carcinoma in Western countries. *Hepatogastroenterology* 1998; **45** Suppl 3: 1206-1213 [PMID: 9730376]

7 **Chiba T**, Matsuzaki Y, Abei M, Shoda J, Aikawa T, Tanaka N, Osuga T. Multivariate analysis of risk factors for hepatocellular carcinoma in patients with hepatitis C virus-related liver cirrhosis. *J Gastroenterol* 1996; **31**: 552-558 [PMID: 8844477 DOI: 10.1007/BF02355056]

8 **Velosa J**, Serejo F, Marinho R, Nunes J, Glória H. Eradication of hepatitis C virus reduces the risk of hepatocellular carcinoma in patients with compensated cirrhosis. *Dig Dis Sci* 2011; **56**: 1853-1861 [PMID: 21374066 DOI: 10.1007/s10620-011-1621-2]

9 **Hsu CS**, Chao YC, Lin HH, Chen DS, Kao JH. Systematic Review: Impact of Interferon-based Therapy on HCV-related Hepatocellular Carcinoma. *Sci Rep* 2015; **5**: 9954 [PMID: 25963067 DOI: 10.1038/srep09954]

10 **Zhang L**, Gwinn M, Hu DJ. Viral hepatitis C gets personal--the value of human genomics to public health. *Public Health Genomics* 2013; **16**: 192-197 [PMID: 23859951 DOI: 10.1159/000352014]

11 **Friedrich-Rust M**, Zeuzem S, Sarrazin C. Current therapy for hepatitis C. *Int J Colorectal Dis* 2007; **22**: 341-349 [PMID: 16175369 DOI: 10.1007/s00384-005-0038-9]

12 **Peveling-Oberhag J**, Zeuzem S, Hofmann WP. Antiviral therapy of chronic hepatitis C in patients with advanced liver disease and after liver transplantation. *Med Microbiol Immunol* 2010; **199**: 1-10 [PMID: 19902246 DOI: 10.1007/s00430-009-0131-8]

13 **Levitsky J**, Fiel MI, Norvell JP, Wang E, Watt KD, Curry MP, Tewani S, McCashland TM, Hoteit MA, Shaked A, Saab S, Chi AC, Tien A, Schiano TD. Risk for immune-mediated graft dysfunction in liver transplant recipients with recurrent HCV infection treated with pegylated interferon. *Gastroenterology* 2012; **142**: 1132-1139.e1 [PMID: 22285805 DOI: 10.1053/j.gastro.2012.01.030]

14 **Han DS**, Hahm B, Rho HM, Jang SK. Identification of the protease domain in NS3 of hepatitis C virus. *J Gen Virol* 1995; **76** (Pt 4):

985-993 [PMID: 9049347 DOI: 10.1099/0022-1317-76-4-985]
15 **Welzel TM**, Dultz G, Zeuzem S. Interferon-free antiviral combination therapies without nucleosidic polymerase inhibitors. *J Hepatol* 2014; **61**: S98-S107 [PMID: 25443350 DOI: 10.1016/j.jhep.2014.08.014]
16 **Sarrazin C**, Hézode C, Zeuzem S, Pawlotsky JM. Antiviral strategies in hepatitis C virus infection. *J Hepatol* 2012; **56** Suppl 1: S88-100 [PMID: 22300469 DOI: 10.1016/S0168-8278(12)60010-5]
17 **Abergel A**, Asselah T, Metivier S, Kersey K, Jiang D, Mo H, Pang PS, Samuel D, Loustaud-Ratti V. Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. *Lancet Infect Dis* 2016; **16**: 459-464 [PMID: 26803446]
18 **Bourlière M**, Bronowicki JP, de Ledinghen V, Hézode C, Zoulim F, Mathurin P, Tran A, Larrey DG, Ratziu V, Alric L, Hyland RH, Jiang D, Doehle B, Pang PS, Symonds WT, Subramanian GM, McHutchison JG, Marcellin P, Habersetzer F, Guyader D, Grangé JD, Loustaud-Ratti V, Serfaty L, Metivier S, Leroy V, Abergel A, Pol S. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *Lancet Infect Dis* 2015; **15**: 397-404 [PMID: 25773757 DOI: 10.1016/S1473-3099(15)70050-2]
19 **Charlton M**, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS, Fried MW, Terrault NA, O'Leary JG, Vargas HE, Kuo A, Schiff E, Sulkowski MS, Gilroy R, Watt KD, Brown K, Kwo P, Pungpapong S, Korenblat KM, Muir AJ, Teperman L, Fontana RJ, Denning J, Arterburn S, Dvory-Sobol H, Brandt-Sarif T, Pang PS, McHutchison JG, Reddy KR, Afdhal N. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. *Gastroenterology* 2015; **149**: 649-659 [PMID: 25985734 DOI: 10.1053/j.gastro.2015.05.010]
20 **Curry MP**, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, Reddy KR, Lawitz E, Flamm SL, Schiano T, Teperman L, Fontana R, Schiff E, Fried M, Doehle B, An D, McNally J, Osinusi A, Brainard DM, McHutchison JG, Brown RS, Charlton M. Sofosbuvir and Velpatasvir for HCV in Patients with Decompensated Cirrhosis. *N Engl J Med* 2015; **373**: 2618-2628 [PMID: 26569658 DOI: 10.1056/NEJMoa1512614]
21 **Curry MP**, Forns X, Chung RT, Terrault NA, Brown R, Fenkel JM, Gordon F, O'Leary J, Kuo A, Schiano T, Everson G, Schiff E, Befeler A, Gane E, Saab S, McHutchison JG, Subramanian GM, Symonds WT, Denning J, McNair L, Arterburn S, Svarovskaia E, Moonka D, Afdhal N. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. *Gastroenterology* 2015; **148**: 100-107.e1 [PMID: 25261839 DOI: 10.1053/j.gastro.2014.09.023]
22 **Feld JJ**, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, Abergel A, Mangia A, Lai CL, Chan HL, Mazzotta F, Moreno C, Yoshida E, Shafran SD, Towner WJ, Tran TT, McNally J, Osinusi A, Svarovskaia E, Zhu Y, Brainard DM, McHutchison JG, Agarwal K, Zeuzem S. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. *N Engl J Med* 2015; **373**: 2599-2607 [PMID: 26571066 DOI: 10.1056/NEJMoa1512610]
23 **Feld JJ**, Moreno C, Trinh R, Tam E, Bourgeois S, Horsmans Y, Elkhashab M, Bernstein DE, Younes Z, Reindollar RW, Larsen L, Fu B, Howieson K, Polepally AR, Pangerl A, Shulman NS, Poordad F. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12weeks. *J Hepatol* 2016; **64**: 301-307 [PMID: 26476290 DOI: 10.1016/j.jhep.2015.10.005]
24 **Forns X**, Gordon SC, Zuckerman E, Lawitz E, Calleja JL, Hofer H, Gilbert C, Palcza J, Howe AY, DiNubile MJ, Robertson MN, Wahl J, Barr E, Buti M. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. *J Hepatol* 2015; **63**: 564-572 [PMID: 25895428 DOI: 10.1016/j.jhep.2015.04.009]
25 **Foster GR**, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, Lawitz E, Thompson A, Shiffman ML, Cooper C, Towner WJ, Conway B, Ruane P, Bourlière M, Asselah T, Berg T, Zeuzem S, Rosenberg W, Agarwal K, Stedman CA, Mo H, Dvory-Sobol H, Han L, Wang J, McNally J, Osinusi A, Brainard DM, McHutchison JG, Mazzotta F, Tran TT, Gordon SC, Patel K, Reau N, Mangia A, Sulkowski M. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. *N Engl J Med* 2015; **373**: 2608-2617 [PMID: 26575258 DOI: 10.1056/NEJMoa1512612]
26 **Kumada H**, Chayama K, Rodrigues L, Suzuki F, Ikeda K, Toyoda H, Sato K, Karino Y, Matsuzaki Y, Kioka K, Setze C, Pilot-Matias T, Patwardhan M, Vilchez RA, Burroughs M, Redman R. Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir for hepatitis C virus genotype 1b-infected Japanese patients with or without cirrhosis. *Hepatology* 2015; **62**: 1037-1046 [PMID: 26147154 DOI: 10.1002/hep.27972]
27 **Lawitz E**, Matusow G, DeJesus E, Yoshida EM, Felizarta F, Ghalib R, Godofsky E, Herring RW, Poleynard G, Sheikh A, Tobias H, Kugelmas M, Kalmeijer R, Peeters M, Lenz O, Fevery B, De La Rosa G, Scott J, Sinha R, Witek J. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: A phase 3 study (OPTIMIST-2). *Hepatology* 2016; **64**: 360-369 [PMID: 26704148 DOI: 10.1002/hep.28422]
28 **Lawitz E**, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyader D, Alric L, Bronowicki JP, Lester L, Sievert W, Ghalib R, Balart L, Sund F, Lagging M, Dutko F, Shaughnessy M, Hwang P, Howe AY, Wahl J, Robertson M, Barr E, Haber B. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet* 2015; **385**: 1075-1086 [PMID: 25467591 DOI: 10.1016/S0140-6736(14)61795-5]
29 **Lawitz E**, Makara M, Akarca US, Thuluvath PJ, Preotescu LL, Varunok P, Morillas RM, Hall C, Mobashery N, Redman R, Pilot-Matias T, Vilchez RA, Hézode C. Efficacy and Safety of Ombitasvir, Paritaprevir, and Ritonavir in an Open-Label Study of Patients With Genotype 1b Chronic Hepatitis C Virus Infection With and Without Cirrhosis. *Gastroenterology* 2015; **149**: 971-80.e1 [PMID: 26170136 DOI: 10.1053/j.gastro.2015.07.001]
30 **Leroy V**, Angus P, Bronowicki JP, Dore GJ, Hezode C, Pianko S, Pol S, Stuart K, Tse E, McPhee F, Bhore R, Jimenez-Exposito MJ, Thompson AJ. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). *Hepatology* 2016; **63**: 1430-1441 [PMID: 26822022 DOI: 10.1002/hep.28473]
31 **Manns M**, Forns X, Samuel D, Denning J, Arterburn S, Brandt-Sarif T, Dvory-Sobol H, Pang P, McHutchison J, Gane E, Mutimer D. Ledipasvir/sofosbuvir with ribavirin is safe and efficacious in decompensated and post-liver transplant patients with HCV infection: preliminary results of the SOLAR-2 trial. Proceedings of the 50th Annual Meeting of the European Association for the Study of the Liver; 2015 April 18-22. Vienna, Austria, 2015
32 **Mizokami M**, Yokosuka O, Takehara T, Sakamoto N, Korenaga M, Mochizuki H, Nakane K, Enomoto H, Ikeda F, Yanase M, Toyoda H, Genda T, Umemura T, Yatsuhashi H, Ide T, Toda N, Nirei K, Ueno Y, Nishigaki Y, Betular J, Gao B, Ishizaki A, Omote M, Mo H, Garrison K, Pang PS, Knox SJ, Symonds WT, McHutchison JG, Izumi N, Omata M. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. *Lancet Infect Dis* 2015; **15**: 645-653 [PMID: 25863559 DOI: 10.1016/S1473-3099(15)70099-X]
33 **Nelson DR**, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, Freilich BF, Younes ZH, Harlan W, Ghalib R, Oguchi G, Thuluvath PJ, Ortiz-Lasanta G, Rabinovitz M, Bernstein D, Bennett M, Hawkins T, Ravendhran N, Sheikh AM, Varunok P, Kowdley KV, Hennicken D, McPhee F, Rana K, Hughes EA. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis

C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* 2015; **61**: 1127-1135 [PMID: 25614962 DOI: 10.1002/hep.27726]

34 **Omata M**, Nishiguchi S, Ueno Y, Mochizuki H, Izumi N, Ikeda F, Toyoda H, Yokosuka O, Nirei K, Genda T, Umemura T, Takehara T, Sakamoto N, Nishigaki Y, Nakane K, Toda N, Ide T, Yanase M, Hino K, Gao B, Garrison KL, Dvory-Sobol H, Ishizaki A, Omote M, Brainard D, Knox S, Symonds WT, McHutchison JG, Yatsuhashi H, Mizokami M. Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. *J Viral Hepat* 2014; **21**: 762-768 [PMID: 25196837 DOI: 10.1111/jvh.12312]

35 **Poordad F**, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, Shiffman ML, Wedemeyer H, Berg T, Yoshida EM, Forns X, Lovell SS, Da Silva-Tillmann B, Collins CA, Campbell AL, Podsadecki T, Bernstein B. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014; **370**: 1973-1982 [PMID: 24725237 DOI: 10.1056/NEJMoa1402869]

36 **Poordad F**, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, McPhee F, Hughes EA, Noviello S, Swenson ES. Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or post-transplant recurrence: ALLY-1 phase 3 study. Proceedings of the 50th Annual Meeting of the European Association for the Study of the Liver; 2015 April 22-26. Vienna, Austria, 2015

37 **Poordad F**, Bennett M, Sepe TE, Cohen E, Reindollar RW, Everson G, Phillips RW, Siddique A, Sullivan JG, Box TD, Fu B, Pilot-Mati T, Abunimeh M, Cohen DE, Younes Z. QUARTZ-I: Retreatment of HCV Genotype 1 DAA-failures With Ombitasvir/Paritaprevir/r, Dasabuvir, and Sofosbuvir Proceedings of the 66th Annual Meeting of the American Association for the Study of Liver Diseases; 2015 Nov 13-17. Boston, MA, United States, 2015

38 **Wyles D**, Pockros P, Morelli G, Younes Z, Svarovskaia E, Yang JC, Pang PS, Zhu Y, McHutchison JG, Flamm S, Lawitz E. Ledipasvir-sofosbuvir plus ribavirin for patients with genotype 1 hepatitis C virus previously treated in clinical trials of sofosbuvir regimens. *Hepatology* 2015; **61**: 1793-1797 [PMID: 25846014 DOI: 10.1002/hep.27814]

39 **Zeuzem S**, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, Illeperuma A, Svarovskaia E, Brainard DM, Symonds WT, Subramanian GM, McHutchison JG, Weiland O, Reesink HW, Ferenci P, Hézode C, Esteban R. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; **370**: 1993-2001 [PMID: 24795201 DOI: 10.1056/NEJMoa1316145]

40 **Zeuzem S**, Ghalib R, Reddy KR, Pockros PJ, Ben Ari Z, Zhao Y, Brown DD, Wan S, DiNubile MJ, Nguyen BY, Robertson MN, Wahl J, Barr E, Butterton JR. Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial. *Ann Intern Med* 2015; **163**: 1-13 [PMID: 25909356 DOI: 10.7326/M15-0785]

41 **Welzel TM**, Herzer K, Ferenci P, Petersen J, Gschwantler M, Cornberg M, Berg T, Spengler U, Weiland O, Van der Valk M, Klinker H, Rockstroh J, Ingiliz P, Peck-Radosavljevic M, Jimenez-Exposito MJ, Zeuzem S. P0772: Daclatasvir plus sofosbuvir with or without ribavirin for the treatment of HCV in patients with severe liver disease: Interim results of a multicenter compassionate use program. *J Hepatol* 2015; **62**: S619-S620 [DOI: 10.1016/s0168-8278(15)30975-2]

42 **Reddy KR**, Bourlière M, Sulkowski M, Omata M, Zeuzem S, Feld JJ, Lawitz E, Marcellin P, Welzel TM, Hyland R, Ding X, Yang J, Knox S, Pang P, Dvory-Sobol H, Subramanian GM, Symonds W, McHutchison JG, Mangia A, Gane E, Mizokami M, Pol S, Afdhal N. Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: An integrated safety and efficacy analysis. *Hepatology* 2015; **62**: 79-86 [PMID: 25846144 DOI: 10.1002/hep.27826]

43 **Saxena V**, Nyberg L, Pauly M, Dasgupta A, Nyberg A, Piasecki B, Winston B, Redd J, Ready J, Terrault NA. Safety and Efficacy of Simeprevir/Sofosbuvir in Hepatitis C-Infected Patients With Compensated and Decompensated Cirrhosis. *Hepatology* 2015; **62**: 715-725 [PMID: 26033798 DOI: 10.1002/hep.27922]

44 **Shiffman ML**, James AM, Long AG, Alexander PC. Treatment of chronic HCV with sofosbuvir and simeprevir in patients with cirrhosis and contraindications to interferon and/or ribavirin. *Am J Gastroenterol* 2015; **110**: 1179-1185 [PMID: 26215530 DOI: 10.1038/ajg.2015.218]

45 **Welzel TM**, Petersen J, Ferenci P, Gschwantler M, Herzer K, Cornberg M, Schott E, Berg T, Spengler U, Weiland O, van der Valk M, Geier A, Rockstroh JK, Peck-Radosavljevic M, Zhao Y, Jimenez Exposito MJ, Zeuzem S. Safety and efficacy of daclatasvir plus sofosbuvir with or without ribavirin for the treatment of chronic HCV genotype 3 infection: Interim results of a multicenter European compassionate use program. Proceedings of the 66th Annual Meeting of the American Association for the Study of Liver Diseases; 2015 November 13-17. San Francisco, CA, USA, 2015

46 **Jensen D**, O`Leary J, Pockros P, Sherman K, Kwo P, Mailliard M, Kowdley K, Muir A, Dickson R, Ramani A, Manns M, Lok A, Akushevich L, Nelson D, Fried M, Group ftH-TS. Safety and efficacy of sofosbuvir-containing regimens for hepatitis C: real-world experience in a diverse, longitudinal observational cohort. [Abstract 45.]. Proceedings of the 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); 2014 November 7-11. Boston, MA, USA, 2014

47 **Coilly A**, Pageaux G, Houssel-Debry P, Duvoux C, Radenne S, de Ledinghen V, Botta-Fridlund D, Vallet-Pichard A, Anty R, Di Martino V, Conti F, Debette-Gratien M, Laurent Alric L, Abergel A, Besch C, Montialoux H, Lebray P, Dharancy S, Durand F, d' Alteroche L, Charier F, Chazouillères O, Dumortier J, Leroy V, Duclos-Vallee J. Improving liver function and delisting of patients awaiting liver transplantation for HCV cirrhosis: do we ask too much to DAA? Proceedings of the Annual Meeting of the American Association for the Study of Liver Diseases; 2015 November 13-17. San Francisco, USA, 2015

48 **Hezode C**, de Ledinghen V, Fontaine H, Zoulim F, Lebray P, Boyer N, Larrey DG, Silvain C, Botta-Fridlund D, Leroy V, Bourlière M, d'Alteroche L, Fouchard-Hubert I, Guyader D, Rosa I, Nguyen-Khac E, Di Martino V, Carrat F, Fedchuk L, Akremi R, Bennai Y, Bronowicki J-P. Daclatasvir plus sofosbuvir with or without ribavirin in genotype 3 patients from a large French multicenter compassionate use program. Proceedings of the 66th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); 2015 November 13-17. San Francisco, California, USA, 2015

49 **Foster GR**, Irving WL, Cheung MC, Walker AJ, Hudson BE, Verma S, McLauchlan J, Mutimer DJ, Brown A, Gelson WT, MacDonald DC, Agarwal K. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol* 2016; **64**: 1224-1231 [PMID: 26829205 DOI: 10.1016/j.jhep.2016.01.029]

50 **Cho Y**, Cho EJ, Lee JH, Yu SJ, Yoon JH, Kim YJ. Sofosbuvir-based therapy for patients with chronic hepatitis C: Early experience of its efficacy and safety in Korea. *Clin Mol Hepatol* 2015; **21**: 358-364 [PMID: 26770924 DOI: 10.3350/cmh.2015.21.4.358]

51 **Hézode C**, Chevaliez S, Scoazec G, Soulier A, Varaut A, Bouvier-Alias M, Ruiz I, Roudot-Thoraval F, Mallat A, Féray C, Pawlotsky JM. Retreatment with sofosbuvir and simeprevir of patients with hepatitis C virus genotype 1 or 4 who previously failed a daclatasvir-containing regimen. *Hepatology* 2016; **63**: 1809-1816 [PMID: 26853230 DOI: 10.1002/hep.28491]

52 **Lawitz E**, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, Symonds WT, McHutchison JG, Membreno FE. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet* 2014; **383**: 515-523 [PMID: 24209977 DOI: 10.1016/S0140-6736(13)62121-2]

53 **Afdhal N**, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M,

Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1889-1898 [PMID: 24725239 DOI: 10.1056/NEJMoa1402454]

54 **Afdhal N**, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, Ghalib R, Gitlin N, Herring R, Lalezari J, Younes ZH, Pockros PJ, Di Bisceglie AM, Arora S, Subramanian GM, Zhu Y, Dvory-Sobol H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1483-1493 [PMID: 24725238 DOI: 10.1056/NEJMoa1316366]

55 **Kowdley KV**, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, Shiffman ML, Schiff E, Ghalib R, Ryan M, Rustgi V, Chojkier M, Herring R, Di Bisceglie AM, Pockros PJ, Subramanian GM, An D, Svarovskaia E, Hyland RH, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Pound D, Fried MW. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014; **370**: 1879-1888 [PMID: 24720702 DOI: 10.1056/NEJMoa1402355]

56 **Feld JJ**, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, Weiland O, Aguilar H, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014; **370**: 1594-1603 [PMID: 24720703 DOI: 10.1056/NEJMoa1315722]

57 **Zeuzem S**, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourlière M, Sulkowski MS, Wedemeyer H, Tam E, Desmond P, Jensen DM, Di Bisceglie AM, Varunok P, Hassanein T, Xiong J, Pilot-Matias T, DaSilva-Tillmann B, Larsen L, Podsadecki T, Bernstein B. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014; **370**: 1604-1614 [PMID: 24720679 DOI: 10.1056/NEJMoa1401561]

58 **Ferenci P**, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, Tam E, Marinho RT, Tsai N, Nyberg A, Box TD, Younes Z, Enayati P, Green S, Baruch Y, Bhandari BR, Caruntu FA, Sepe T, Chulanov V, Janczewska E, Rizzardini G, Gervain J, Planas R, Moreno C, Hassanein T, Xie W, King M, Podsadecki T, Reddy KR. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* 2014; **370**: 1983-1992 [PMID: 24795200 DOI: 10.1056/NEJMoa1402338]

59 **Hézode C**, Asselah T, Reddy KR, Hassanein T, Berenguer M, Fleischer-Stepniewska K, Marcellin P, Hall C, Schnell G, Pilot-Matias T, Mobashery N, Redman R, Vilchez RA, Pol S. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. *Lancet* 2015; **385**: 2502-2509 [PMID: 25837829 DOI: 10.1016/S0140-6736(15)60159-3]

60 **Sulkowski MS**, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasela DM. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014; **370**: 211-221 [PMID: 24428467 DOI: 10.1056/NEJMoa1306218]

61 **Alqahtani SA**, Afdhal N, Zeuzem S, Gordon SC, Mangia A, Kwo P, Fried M, Yang JC, Ding X, Pang PS, McHutchison JG, Pound D, Reddy KR, Marcellin P, Kowdley KV, Sulkowski M. Safety and tolerability of ledipasvir/sofosbuvir with and without ribavirin in patients with chronic hepatitis C virus genotype 1 infection: Analysis of phase III ION trials. *Hepatology* 2015; **62**: 25-30 [PMID: 25963890 DOI: 10.1002/hep.27890]

62 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines. Recommendations on treatment of hepatitis C. Geneva, Switzerland, 2015

63 **American Association for the Study of Liver Diseases**. HCV guidelines. Alexandria, Virginia, USA, 2016

64 **Keating GM**. Elbasvir/Grazoprevir: First Global Approval. *Drugs* 2016; **76**: 617-624 [PMID: 26943930 DOI: 10.1007/s40265-016-0558-3]

65 **Jacobson IM**, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Pianko S, Nelson DR. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; **368**: 1867-1877 [PMID: 23607593 DOI: 10.1056/NEJMoa1214854]

66 **Lawitz E**, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368**: 1878-1887 [PMID: 23607594 DOI: 10.1056/NEJMoa1214853]

67 **Dieterich D**, Bacon B, Flamm S, Kowdley K, Milligan S, Tsai N, Younossi Z, Lawitz E. Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network - Academic and community treatment of a real-world, heterogeneous population. Proceedings of the AASLD; 2014 Nov 8-11. Boston, MA, USA, 2014

68 **Foster GR**, Pianko S, Brown A, Forton D, Nahass RG, George J, Barnes E, Brainard DM, Massetto B, Lin M, Han B, McHutchison JG, Subramanian GM, Cooper C, Agarwal K. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. *Gastroenterology* 2015; **149**: 1462-1470 [PMID: 26248087 DOI: 10.1053/j.gastro.2015.07.043]

69 **Ferenci P**, Kozbial K, Mandorfer M, Hofer H. HCV targeting of patients with cirrhosis. *J Hepatol* 2015; **63**: 1015-1022 [PMID: 26100497 DOI: 10.1016/j.jhep.2015.06.003]

70 **Flamm S**, Everson G, Charlton M. Ledipasvir/Sofosbuvir with Ribavirin for the Treatment of HCV in Patients with Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study. Proceedings of the 65th Annual Meeting of the American Association for the Study of Liver diseases; 2014 November 7-11. Boston, USA, 2014

71 **Welker MW**, Luhne S, Lange CM, Vermehren J, Farnik H, Herrmann E, Welzel T, Zeuzem S, Sarrazin C. Lactic acidosis in patients with hepatitis C virus cirrhosis and combined ribavirin/sofosbuvir treatment. *J Hepatol* 2016; **64**: 790-799 [PMID: 26658684 DOI: 10.1016/j.jhep.2015.11.034]

72 **Manns M**, Samuel D, Gane EJ, Mutimer D, McCaughan G, Buti M, Prieto M, Calleja JL, Peck-Radosavljevic M, Müllhaupt B, Agarwal K, Angus P, Yoshida EM, Colombo M, Rizzetto M, Dvory-Sobol H, Denning J, Arterburn S, Pang PS, Brainard D, McHutchison JG, Dufour JF, Van Vlierberghe H, van Hoek B, Forns X; SOLAR-2 investigators. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. *Lancet Infect Dis* 2016; **16**: 685-697 [PMID: 26907736 DOI: 10.1016/S1473-3099(16)00052-9]

73 Health USNIo. A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination Administered in Patients Infected With Chronic HCV for Use in the Peri-Operative Liver Transplantation Setting. 2016

74 **Coilly A**, Roche B, Duclos-Vallée JC, Samuel D. Optimal therapy in hepatitis C virus liver transplant patients with direct acting antivirals. *Liver Int* 2015; **35** Suppl 1: 44-50 [PMID: 25377540 DOI: 10.1111/liv.12728]

75 **Gugenheim J**, Baldini E, Mazza D, Fabiani P, St Paul MC, Goubaux B, Ouzan D, Mouiel J. Recurrence of hepatitis C virus after liver transplantation. *Transpl Int* 1994; **7** Suppl 1: S224-S226 [PMID: 11271209 DOI: 10.1111/j.1432-2277.1994.tb01352.x]

76 **Dixon LR**, Crawford JM. Early histologic changes in fibrosing

cholestatic hepatitis C. *Liver Transpl* 2007; **13**: 219-226 [PMID: 17205558 DOI: 10.1002/lt.21011]
77 **Brown RS**, O'Leary JG, Reddy KR, Kuo A, Morelli GJ, Burton JR, Stravitz RT, Durand C, Di Bisceglie AM, Kwo P, Frenette CT, Stewart TG, Nelson DR, Fried MW, Terrault NA. Interferon-free therapy for genotype 1 hepatitis C in liver transplant recipients: Real-world experience from the hepatitis C therapeutic registry and research network. *Liver Transpl* 2016; **22**: 24-33 [PMID: 26519873 DOI: 10.1002/lt.24366]
78 **Hanouneh IA**, Miller C, Aucejo F, Lopez R, Quinn MK, Zein NN. Recurrent hepatitis C after liver transplantation: on-treatment prediction of response to peginterferon/ribavirin therapy. *Liver Transpl* 2008; **14**: 53-58 [PMID: 18161839 DOI: 10.1002/lt.21312]
79 **Fiel MI**, Schiano TD. Plasma cell hepatitis (de-novo autoimmune hepatitis) developing post liver transplantation. *Curr Opin Organ Transplant* 2012; **17**: 287-292 [PMID: 22498651 DOI: 10.1097/MOT.0b013e3283536622]
80 **Coilly A**, Dumortier J, Botta-Fridlund D, Latournerie M, Leroy V, Pageaux GP, Agostini H, Giostra E, Moreno C, Roche B, Antonini TM, Guillaud O, Lebray P, Radenne S, Saouli AC, Calmus Y, Alric L, Debette-Gratien M, De Ledinghen V, Durand F, Duvoux C, Samuel D, Duclos-Vallée JC. Multicenter Experience with Boceprevir or Telaprevir to Treat Hepatitis C Recurrence after Liver Transplantation: When Present Becomes Past, What Lessons for Future? *PLoS One* 2015; **10**: e0138091 [PMID: 26394142 DOI: 10.1371/journal.pone.0138091]
81 **Coilly A**, Furlan V, Roche B, Barau C, Noël C, Bonhomme-Faivre L, Antonini TM, Roque-Afonso AM, Samuel D, Taburet AM, Duclos-Vallée JC. Practical management of boceprevir and immunosuppressive therapy in liver transplant recipients with hepatitis C virus recurrence. *Antimicrob Agents Chemother* 2012; **56**: 5728-5734 [PMID: 22908172 DOI: 10.1128/AAC.01151-12]
82 **Charlton M**, Gane E, Manns MP, Brown RS, Curry MP, Kwo PY, Fontana RJ, Gilroy R, Teperman L, Muir AJ, McHutchison JG, Symonds WT, Brainard D, Kirby B, Dvory-Sobol H, Denning J, Arterburn S, Samuel D, Forns X, Terrault NA. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. *Gastroenterology* 2015; **148**: 108-117 [PMID: 25304641 DOI: 10.1053/j.gastro.2014.10.001]
83 **Reddy KR**, Everson GT, Flamm SL, Denning JM, Arterburn S, Brandt-Sarif T, Pang PS, McHutchison JG, Curry MP, Charlton M. Ledipasvir/Sofosbuvir with Ribavirin for the Treatment of HCV in Patients with Post Transplant Recurrence: Preliminary Results of a Prospective, Multicenter Study. Proceedings of the 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); 2014 November 7-11. Boston, MA, USA, 2014
84 **Kwo PY**, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R, Gordon F, Levitsky J, Terrault NA, Burton JR, Xie W, Setze C, Badri P, Pilot-Matias T, Vilchez RA, Forns X. An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med* 2014; **371**: 2375-2382 [PMID: 25386767 DOI: 10.1056/NEJMoa1408921]
85 **Forns X**, Charlton M, Denning J, McHutchison JG, Symonds WT, Brainard D, Brandt-Sarif T, Chang P, Kivett V, Castells L, Prieto M, Fontana RJ, Baumert TF, Coilly A, Londoño MC, Habersetzer F. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. *Hepatology* 2015; **61**: 1485-1494 [PMID: 25557906 DOI: 10.1002/hep.27681]
86 **Pungpapong S**, Aqel B, Leise M, Werner KT, Murphy JL, Henry TM, Ryland K, Chervenak AE, Watt KD, Vargas HE, Keaveny AP. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. *Hepatology* 2015; **61**: 1880-1886 [PMID: 25722203 DOI: 10.1002/hep.27770]
87 **Pellicelli AM**, Montalbano M, Lionetti R, Durand C, Ferenci P, D'Offizi G, Knop V, Telese A, Lenci I, Andreoli A, Zeuzem S, Angelico M. Sofosbuvir plus daclatasvir for post-transplant recurrent hepatitis C: potent antiviral activity but no clinical benefit if treatment is given late. *Dig Liver Dis* 2014; **46**: 923-927 [PMID: 24997638 DOI: 10.1016/j.dld.2014.06.004]
88 **Herzer K**, Papadopoulos-Köhn A, Walker A, Achterfeld A, Paul A, Canbay A, Timm J, Gerken G. Daclatasvir, Simeprevir and Ribavirin as a Promising Interferon-Free Triple Regimen for HCV Recurrence after Liver Transplant. *Digestion* 2015; **91**: 326-333 [PMID: 25999053 DOI: 10.1159/000382075]
89 **Saab S**, Greenberg A, Li E, Bau SN, Durazo F, El-Kabany M, Han S, Busuttil RW. Sofosbuvir and simeprevir is effective for recurrent hepatitis C in liver transplant recipients. *Liver Int* 2015; **35**: 2442-2447 [PMID: 25913321 DOI: 10.1111/liv.12856]
90 **Punzalan CS**, Barry C, Zacharias I, Rodrigues J, Mehta S, Bozorgzadeh A, Barnard GF. Sofosbuvir plus simeprevir treatment of recurrent genotype 1 hepatitis C after liver transplant. *Clin Transplant* 2015; **29**: 1105-1111 [PMID: 26358816 DOI: 10.1111/ctr.12634]
91 **Shiraga T**, Matsuda H, Nagase K, Iwasaki K, Noda K, Yamazaki H, Shimada T, Funae Y. Metabolism of FK506, a potent immunosuppressive agent, by cytochrome P450 3A enzymes in rat, dog and human liver microsomes. *Biochem Pharmacol* 1994; **47**: 727-735 [PMID: 7510480 DOI: 10.1016/0006-2952(94)90136-8]
92 **Cakaloglu Y**, Tredger JM, Devlin J, Williams R. Importance of cytochrome P-450IIIA activity in determining dosage and blood levels of FK 506 and cyclosporine in liver transplant recipients. *Hepatology* 1994; **20**: 309-316 [PMID: 7519161 DOI: 10.1002/hep.1840200207]
93 **Pichard L**, Domergue J, Fourtanier G, Koch P, Schran HF, Maurel P. Metabolism of the new immunosuppressor cyclosporin G by human liver cytochromes P450. *Biochem Pharmacol* 1996; **51**: 591-598 [PMID: 8615894 DOI: 10.1016/S0006-2952(95)02175-2]
94 **Kogiso T**, Tokushige K, Hashimoto E, Taniai M, Omori A, Kotera Y, Egawa H, Yamamoto M, Shiratori K. Mycophenolate mofetil may induce prolonged severe anemia during pegylated-interferon/ribavirin/simeprevir therapy in liver transplant recipients. *Clin J Gastroenterol* 2015; **8**: 156-161 [PMID: 25963122 DOI: 10.1007/s12328-015-0570-2]
95 **Afdhal N**, Everson G, Calleja JL, McCaughan G, Symonds WT, Denning J, McNair L, McHutchison JG, Arterburn S, Charlton M, Reddy R, Asselah T, Gane E, Forns X. Sofosbuvir and Ribavirin for the treament of chronic HCV with cirrhosis and portal hypertension with and without decompensation: early virologic response and safety. *J Hepatol* 2014; **60**: S28 [DOI: 10.1016/S0168-8278(14)60070-2]
96 **Wilder JM**, Muir AJ. Strategies for treating chronic HCV infection in patients with cirrhosis: latest evidence and clinical outcomes. *Ther Adv Chronic Dis* 2015; **6**: 314-327 [PMID: 26568808 DOI: 10.1177/2040622315603642]

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