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REVIEW

Interferon-free antiviral treatment of chronic hepatitis C in the transplant setting

Sandra Beinhardt, Markus Peck-Radosavljevic, Harald Hofer and Peter Ferenci

Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

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Correspondence
Peter Ferenci, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria.
Tel.: +43 1 40400 47450;
fax: +43 1 40400 47350;
e-mail: peter.ferenci@meduniwien.ac.at

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Summary

Interferon-based regimens with first-generation protease inhibitors have a limited efficacy and an unfavorable safety profile. Combination therapies with two or more second-generation direct-acting antivirals plus/minus ribavirin revolutionized treatment strategies in patients chronically infected with hepatitis C virus. In this rapidly evolving era, patients in the transplant setting benefit from interferon-free treatment regimens. Scientific societies can barely keep up with this development, making it necessary to update the clinical guidelines by the American and European Associations for the Study of Liver Diseases within short periods. This review presents and discusses the currently available data of the use of interferon-free treatment in the setting of liver transplantation. However, costs, different reimbursement strategies, and health-care options cannot be answered by guidelines and recommendations from scientific societies. Further investigator-initiated trials are needed to individualize treatment concepts.

Introduction

Liver cirrhosis due to chronic hepatitis C virus (HCV) infection is the leading indication for liver transplantation (OLT) in the Western countries, Japan, and the Middle East [1,2]. Reinfection of the graft occurs almost in all patients after transplantation. The main characteristic of hepatitis C recurrence after transplantation is the accelerated course of disease, when compared to immunocompetent patients [3–8]. Eradication of HCV 'before' OLT will prevent post-transplant recurrence, associated with impaired graft and patient survival [9]. Eradication of HCV 'after' OLT is the main independent factor, associated with better prognosis after transplantation. Within the peritransplant setting, the use of peginterferon/ribavirin-(PR) [10] based therapies, including a combination with one of the first-generation protease inhibitors boceprevir (Victrelis®; MSD) or telaprevir (Incivec®/Incivo®; Janssen-Cilag) is limited by their side effect profile in general. In cirrhotic nonresponders to previous PR treatment, sustained virological response (SVR) rates were low [10]. Moreover, triple therapy in the *pre*transplant setting is contraindicated in the presence of decompensated cirrhosis [11,12]. Protease inhibitors are metabolized by CYP450 3A4 [13] and interfere thereby with the dosing of calcineurin inhibitors (Table 1). Furthermore, they also aggravate anemia when used together with ribavirin (RBV) [14].

Both, the European Association for the Study of the Liver (EASL) as well as the American Associations for the Study of Liver Diseases (AASLD) endorsed not to use interferon-based treatment regimens in patients with *de*compensated liver cirrhosis [Child–Pugh (Turcotte) score

Table 1. Drug–Drug interactions (DDIs) of direct-acting antivirals (DAA) with immunosuppressive regimens.

		HCV NS3/4 Protease inhibitors				HCV NS5A Polymerase inhibitors			HCV NS5B Polymerase inhibitors	
	Ribavirin	Boceprevir 800 mg tid	Telaprevir 750 mg tid	Simeprevir 150 mg qd	ABT-450-r 150 mg/100 mg qd	Daclatasvir 60 mg qd	Ledipasvir 90 mg qd	Ombitasvir 25 mg qd	Sofosbuvir 400 mg qd	Dasabuvir 250 mg bid
Route of metabolism; excretion	Hepatic (deribosylation and hydrolysis); renal excretion	CYP3A4, CYP3A5, AKR	CYP3A4	CYP3A4	CYP3A, inhibition by ritonavir; renal excretion	CYP3A4	Not a substrate of CYPP450/ UGT; faeces >98%	ND; AUC & C_{max} increased 62% and 67%, respectively by ritonavir; renal excretion	Not a substrate of CYP450/ UGT; renal excretion	CYP2C8, CYP3A4, CYP2D6 contributes appr. 60%, 30% & 10% to ABT-333 metabolism, respectively
Calcineurin inhibitors										
Cyclosporin	No data	↓CYA dose	↓↓CYA dose	No coadministration according to AASLD recommendations	1/5 of pretreatment-dose	No data	No data	↓1/5 of pretreatment-dose	No dose adjustment	↓1/5 of pretreatment-dose
Tacrolimus	Recommended	↓FK dose	↓↓↓FK dose	No dose adjustment, close monitoring	↓0.5 mg once/ week – 0.2 mg all 3 days	No data	No data	↓0.5 mg once/ week – 0.2 mg all 3 days	No dose adjustment	↓0.5 mg once/ week – 0.2 mg all 3 days
mTOR inhibitors										
Sirolimus	Close monitoring	↓↓SIR dose	↓↓SIR dose	↓↓SIR dose	No data	No data	No data	No data	Recommended	No data
Everolimus	No data	No dose adjustment [48]	No data	No data	No data	No data	No data	No data	No data	No data
Predniso(lo)ne	No data	No dose adjustment, close monitoring	No data	No data	No data	No data	No data	No data	No data	No data
Anti HCV treatment										
PegInterferon	Recommended	Recommended	Recommended,	Recommended	n.a.	Recommended	No data	n.a.	Recommended	n.a.
Ribavirin		Recommended	increasing ribavirin concentration, close monitoring	Recommended	Close monitoring	Recommended	No data	Close monitoring	Recommended	Close monitoring

HCV, Hepatitis C virus; CYA, cyclosporin; FK, tacrolimus; SIR, sirolimus; n.a., not applicable; ND, no data; modified from Miro *et al.* [78]; Kwo *et al.* [41]; https://www.hcvdruginfo.ca.

(CPS) B and C] or after OLT in their recent recommendations [15,16].

With the approval of sofosbuvir (SOF, Sovaldi®; Gilead) IFN-free treatment regimens became available for patients with end-stage liver disease (ESLD) or after OLT. Meanwhile, other DAAs [Simeprevir (Olysio®), Janssen-Cilag; Daclatasvir (Daklinza®), Bristol-Myers Squibb], the fixed dose combinations (FDC) of SOF *plus* ledipasvir (Harvoni®; Gilead), and the '3D' [paritaprevir/ritonavir-boosted *plus* ombitasvir *plus* dasabuvir (Viekira Pak®/US, Viekirax® *plus* Exviera®/EU; AbbVie)] combination have been approved. Thus, a broad armamentarium of therapeutic options for patients with chronic hepatitis C pre- and post-liver transplantation became available.

Treatment options in patients awaiting transplantation

Priority objective of antiviral therapy within this patient population is to prevent graft reinfection after transplantation.

All-oral interferon-free DAA-based regimens – pretransplant setting

Antiviral treatment of patients with compensated cirrhosis on waiting list

A considerable percentage of patients have coexistent hepatocellular carcinoma (HCC) but still good liver function. Pre-emptive antiviral therapy is aiming for prevention of post-OLT HCV recurrence. So far, patients with compensated cirrhosis (CPS:A) had the option of treatment with pegylated IFN/RBV combined with boceprevir or telaprevir. SVR was achieved in a substantial proportion of GT1 patients [17–21], but were low in cirrhotic null-responders to previous PR dual therapy [10]. Nevertheless, this treatment remains an option in well-compensated cirrhotic patients listed for transplantation due to HCC.

Most IFN-free regimens were assessed in patients with compensated cirrhosis infected with GT1 (Table 2). SVR12 rates in cirrhotic patients, participating in phase-III trials, evaluating SOF/ledipasvir FDC ± RBV for 12 vs. 24 weeks, ranged from 85% to 100% [22–24]. In treatment-naive cirrhotics, SVR rates were not dissimilar if patients were treated for 12 weeks of 24 weeks; extension of therapy duration to 24 weeks may be considered in treatment-experienced cirrhotics as SVR rates differed significantly (86% vs. 100% [19]). Similarly, differing SVR rates [92% (12 weeks) vs. 96% (24 weeks); $P = 0.09$] were assessed in the only performed phase-III trial including solely cirrhotic patients hitherto, evaluating the FDC of ritonavir-boosted paritaprevir + ombitasvir + dasabuvir (3D) with RBV [25]. The combination of daclatasvir (DCV) with asunaprevir (ASV) in treatment-naïve or treatment-experienced and IFN-ineligible and IFN-intolerant patients with compensated cirrhosis (CPS:A) for 24 weeks resulted in SVR rates ranging from 81% to 91%, respectively [26]. HCV genotype 3 has emerged as a particularly difficult to treat HCV genotype, and the results of the initial studies of SOF + RBV in HCV GT3 patients were disappointing [27–29]. While SVR rates of >90% can be achieved in noncirrhotic patients, response rates in cirrhotics are substantially lower. By the combination of SOF with RBV given for 24 weeks to treatment-naive and treatment-experienced patients with compensated cirrhosis, a SVR rate of 86% and 60% was achieved, respectively. In the ALLY-3 study [30], the efficacy and safety of SOF plus DCV for 12 weeks were evaluated. SVR rates in noncirrhotic patients were 91% to 95%, but only 73% and 63% in treatment-naive and treatment-experienced cirrhotic patients. Similar data were obtained in cirrhotic patients treated with SOF/LDV [31].

So far, only one study evaluated IFN-free regimens in cirrhotic patients with HCC, listed for transplantation. Curry *et al.* [32] treated patients (GT: 1–4) with SOF *plus* RBV for up to 48 weeks (median: 17 weeks) on OLT waiting list. On-treatment response was achieved in 54 (93%) patients [lower limit of quantitation (LLOQ): <25 IU/ml; treatment week 4] resulting in 43 (46%) patients with LLOQ at transplantation. Of those 30 (70%) patients remained HCV RNA negative after OLT. Treatment was generally well tolerated, only one patient discontinued due to anemia.

Antiviral treatment of patients with decompensated cirrhosis on the waiting list

Antiviral treatment of patients with advanced liver cirrhosis (CPS:B and CPS:C) has two goals: improving the condition of the patient to a point where he/she can be delisted and in those not improving to prevent post-OLT HCV recurrence. Substantial improvement of liver function after successful treatment with DAAs may even allow delisting of patients without HCC or MELD exceptions from the OLT list. Two studies focused on the IFN-free treatment of patients with decompensated cirrhosis. Afdhal *et al.* [33] randomized 50 patients with portal hypertension and compensated (CPS:A) or decompensated cirrhosis (CPS:B) 1:1 into an immediate treatment (SOF plus RBV for 48 weeks) or an observational period (treatment after 24 weeks of observation). On-treatment response at week 8 was nearly universal. After 24 weeks, platelet count improved among treated CPS:A patients and albumin levels improved in both patient cohorts (CPS:A and CPS:B) when compared to the observational arm. However, treatment did affect the model of end-stage liver disease (MELD) score. In contrast to the observational arm, ascites and hepatic encephalopathy resolved in all treated patients.

Table 2. Published trials: All-oral IFN-free regimens including cirrhotic patients – pretransplant setting.

A: Phase II trials
Phase II

DAA regimen	Trial name/citation	Response to previous IFN-based therapy	PLT count (G/l)	TX duration weeks	Cirrhotics included	HCV genotype	HCV subtype	SVR4	SVR12	SVR 24	Additional information
SOF + RBV	Osinusi *et al.* – NIH SPARE [49]	Naive	75	24	13/26% (F3/F4)	1	1a – 70%			29–50%	50% – weight-based RBV; 29% – low-dose RBV
SOF + RBV	Curry *et al.* [32]	Naive/ experienced – OLT-listed; CPS:A	ns	Up to 48	61/100%	1–4	1a – 39%	54/93% LLOQ	ns	ns	43/46 < LLOQ/ LTX-->30/70% post-TX SVR12
SOF + LDV ± RBV	Gane *et al.* – ELECTRON [50]	Null-responder	ns	12	19/100%	1			70–100%		70% – RBV; 100% + RBV
SOF + LDV ± RBV	Lawitz *et al.* – LONESTAR [51]	NR (PI-based triple)	ns	12	22/55%	1	1a – 85%		95–100%		95% – RBV; 100% + RBV
SOF + SMV ± RBV	Lawitz *et al.* – COSMOS [52]	Naive NR (IFN-dual)	ns ns	12 24	41/25%	1	1a – 78%		91–94%		NR: 91% (21/33); naive: 94% (17/18)
FDV + DBV ± RBV	Zeuzem *et al.* – SOUND C2 [53]	Naive	90	16, 28, 40	33/9%	1			33–67%		According to different regimens
SOF + DCV ± RBV	Sulkowski *et al.* [54]	Naive experienced (IFN-dual/ PI-based triple)	ns	12 vs. 24	32/15%	1–3			100%		
SOF + RBV	Ruane *et al.* [55]	Naïve/ experienced; CPS:A	50	12 vs. 24 naïve experienced	14/23%	4		ns	12 we: 1/33%; 24 we: 3/100% 12 we: 2/50%; 24 we: 4/100%		3 SAEs:chestpain/ abdomian pain/loss of conscoiusness (not related)

B: Phase III trials
Phase III

DAA regimen	Trial name/citation	Response to previous IFN-based therapy	PLT count (G/l)	TX duration weeks	Cirrhotics included	HCV genotype	HCV subtype	SVR4	SVR12	SVR 24	Additional information
SOF + RBV	Lawitz *et al.* – FISSION [27]	Naive	75	12	50/20%	2 + 3			47%		
SOF + RBV	Jacobson *et al.* – POSITRON [28]	IFN-intolerant	na	12	31/15%	2 + 3			61%		

Table 2. continued

B: Phase III trials Phase III DAA regimen	Trial name/citation	Response to previous IFN-based therapy	PLT count (G/l)	TX duration weeks	Cirrhotics included	HCV genotype	HCV subtype	SVR4	SVR12	SVR 24	Additional information
SOF + RBV	Jacobson *et al.* – FUSION [28]	NR (IFN-dual)	50	12 16 12 16	36/35% 32/33% 	2 3 			60% 78% 19% 61%		
SOF + RBV	Zeuzem *et al.* – VALENCE [29]	Naive experienced (IFN-dual)	50	12 24	10/14% 59/22%	2 3			60–100%		GT2: naive – 100%/ experienced – 88% GT3: naive – 92%/ experienced – 60%
SOF/LDV ± RBV	Afdhal *et al.* – ION-1 [22]	Naive	50	12 24	136/16%	1			97% 100%		
SOF/LDV ± RBV	Afdhal *et al.* – ION-2 [23]	Experienced We: 12 + RBV: We: 12 – RBV: We: 24 ± RBV:	50	12 vs. 24	88/20%	1			82–100% 86% 82% 100%		
DCV + ASV	Manns *et al.* – HALLMARK-DUAL [26]	Naive, experienced (IFN-dual), IFN-ineligible/intolerant Naive: Experienced: Ineligible/intolerant:	ns	24	223/30%	1	1b		81–91% 91% 87% 81%		
3D + RBV	Poordad *et al.* – TURQUOISE-II [25]	Naive/experienced (IFN-dual); CPS:A open-label, multicenter; EU/US	60	12 24	380/100%	1			92% 96%		

A + B: SOF: sofosbuvir (Sovaldi®; Gilead); RBV: ribavirin; SOF + LDV: sofosbuvir + ledipasvir (Harvoni®; Gilead); SMV: simeprevir (Olysio®; Janssen-Cilag); FDV: faldaprevir; DBV: deleobuvir; DCV: daclatasvir (Daklinza®; Bristol-Myers Squibb); ASV: asunaprevir; PLT: platelet; TX: therapy; SVR: sustained virological response; LLOQ: lower limit of quantitation; OLT: liver transplantation; CPS: Child–Pugh score; NR: nonresponse; we: weeks.

The SOLAR-1 study included 108 treatment-naive or treatment-experienced cirrhotic patients with CPS:B or CPS:C. They were either HCV genotype 1 or 4 [34]. Patients were randomized (1:1) to receive SOF/LDV plus RBV (starting at 600 mg/day and then escalated) for either 12 or 24 weeks. Patients with a creatinine clearance <40 ml/min were excluded. SVR was achieved in 87% of those in the 12-week arm and 89% of those in the 24-week arm, with comparable SVR rates in patients with CPS:B and CPS:C cirrhosis. The rate of treatment discontinuations due to adverse events was low. Total bilirubin levels decreased, while albumin levels increased in both groups, suggesting improved hepatic function. Although CPS improved in 70% of patients, it remained unchanged in 20% and worsened in 10%. Similarly, MELD score improved in the majority of patients. However, decompensated cirrhosis may worsen the tolerability of RBV, especially in patients with impaired renal function. So far, delisting from OLT list was reported in one patient only [35].

Treatment options in patients after transplantation

All-oral interferon-free DAA-based regimens – post-transplant setting

The first report of successful treatment with an all-oral IFN-free regimen of a patient with fibrosing cholestatic hepatitis (FCH) was published in 2013 [36]. Pellicelli *et al.* [37] reported a compilation of several post-transplant patients with FCH or cirrhosis, treated with SOF/DCV ± RBV. Data suggested that IFN-free combinations are effective, but do not change the 'downhill course' if treatment is initiated too late. Meanwhile, four studies, evaluating diverse DAA combination therapies in liver transplant recipients, have been published.

Sofosbuvir plus ribavirin

Charlton *et al.* [38] evaluated efficacy of SOF *plus* RBV administered for 24 weeks in 40 post-transplant patients (GT-1a: 22, GT-1b: 11, GT-3a: 6, GT-4: 1; treatment-naive/treatment-experienced: 35/5; F0–F2: 15, F3: 9, F4: 16; CPS: A) within a prospective, multicenter, open-label pilot study. Post-OLT SVR12 was achieved in 28 (70%) patients; 12 patients relapsed (GT1: 11 [92%]; F3 + F4: 8 [32%]). No death, graft loss or graft rejection was reported; two patients discontinued treatment due to severe adverse events (SAE; pneumonia; HCC); both were reported as unrelated to study drugs. Most common adverse events were fatigue (30%), diarrhea (28%), headache (25%), and anemia (20%). SOF had no reported interactions with any of the concomitant immunosuppressive agents, including tacrolimus (TAC; 70%), mycophenolate mofetil (35%), predniso(lo)ne (28%), cyclosporine A [(CSA); 25%], and azathioprine (5%). Nevertheless, no predictor for HCV recurrence could be identified.

In a compassionate-use program [39], patients with severe recurrent hepatitis C and decompensated cirrhosis with an estimated life expectancy of 1 year or less were treated with SOF *plus* RBV for 24–48 weeks. Investigators could add peginterferon at their discretion. Of the 104 patients analyzed, 52 had either early severe recurrence (diagnosed <12 months after OLT) or cirrhosis ($N = 52$; diagnosed more than 12 months after OLT). Twelve patients who underwent retransplantation were excluded from the efficacy analysis. Of the 92 assessed patients, 54 (59%) achieved SVR12, with a higher rate (35/48 [73%]) in patients with early severe recurrence. Of particular interest is the high SVR rate (80%) in the 10 FCH patients. In contrast, SVR rate in cirrhotic patients was only 44%. The high relapse rate occurred in spite of an excellent primary antiviral response.

Overall, 123 SAEs occurred in 47% of patients. SAEs associated with hepatic decompensation were observed in 19 patients. Six SAEs in 5 (5%) were considered related to study drug: ascites, diabetes, neutropenia, hemophagocytic syndrome, and medullary aplasia/bone marrow failure. Nine patients experienced renal failure/dysfunction (6 acute renal failure, 1 acute chronic renal failure, 1 renal insufficiency, and 1 acute kidney infection). Eight patients died during treatment or within 30 days of last dose; mainly related to progression of liver disease, severe infections or sepsis, pulmonary conditions, and renal failure. Nevertheless, SOF-based antiviral therapy was broadly safe and substantially effective in patients with HCV recurrence and cirrhosis after transplantation.

Sofosbuvir plus simeprevir (SIM)

One hundred and twenty-eight post-OLT patients were treated at the Mayo Clinic with SOF/SIM ± RBV, 25 of them had F3–F4 [40]. The overall SVR rate was 91%, with lower rates in GT-1a than GT-1b patients. Ribavirin had no impact on the outcome.

In the 'real-world' TARGET study [41], the outcome of 124 post-OLT patients was reported. Patients were treated for 24 weeks ± RBV. SVR rates in GT-1a patients were 82% and 80% with and without RBV, respectively, in GT-1b patients 93% and 94%.

Paritaprevir/r + ombitasvir + dasabuvir plus rivavirin

In the CORAL-1 study [42], 34 post-transplant patients without cirrhosis (mostly F0–F1) were treated with the 3D combination plus RBV for 24 weeks. Majority of patients were GT-1a and treatment-naive after OLT. All patients had undetectable HCV RNA at the end of treatment; SVR12 was achieved in 33 (97%) due to one relapse (2.9%). No death, graft loss or graft rejection was reported. One patient discontinued treatment due to side effects at week 18 (rash, memory impairment, and anxiety) – the

patient achieved SVR12. Most common adverse events were fatigue, cough, and headache. Five patients (15%) required erythropoietin, and none needed blood transfusion. Immunosuppressive medication was TAC (85%) and CSA (15%). Due to the interaction with paritaprevir/r dose of calcineurin inhibitors had to be adjusted according to their trough levels. For most TAC patients, 0.5 and 0.2 mg doses were administered with a median dosing frequency of 10 and 5 days, respectively (Table 1).

Currently, in this rapidly evolving era, scientific societies can barely keep up with recent findings to update 'guidelines' or 'recommendations' [15,16]. Further findings from phase-III or real-life studies are needed to obtain longer lasting guidelines for treatment strategies in this population. Specifically, more data are needed to select the proper duration of treatment and to identify patients who will still need RBV.

Ongoing studies

Overall data of about 900 post-transplant patients were reported so far (Table 3), but most of the findings were presented as results of interim analyses of ongoing studies. Results were excellent, but the included proportion of patients with decompensated cirrhosis is still small. Moreover, the evaluated study population is extremely heterogeneous: patients varied according to fibrosis stage, genotypes, pretreatment platelet counts, and whether they were treatment-naive or treatment-experienced. Furthermore, treatment duration varied from 12 up to 48 weeks, given with or without RBV.

Findings from ongoing studies as well as named patient- and early access programs will further increase the understanding for the treatment and necessity of individualization within the post-transplant cohort (Table 3).

Generally, treatment with diverse combinations of DAAs is effective and safe, even in patients with severe HCV recurrence and *(de)*compensated cirrhosis. An important observation of these studies is the finding of recovered liver function after successful HCV eradication, documented by improved MELD scores and increased serum albumin levels [38,42,43]. However, several questions remain to be studied such as timing and optimal duration of antiviral treatment in diverse DAA combinations, as well as the optimal dosing of each drug in patients with decompensated cirrhosis and poor liver function. The pharmacokinetics (PK) of most DAAs given alone or in various combinations has not been addressed in patients with far advanced liver diseases sufficiently; thus, the optimal dose of each drug in this patient group is unknown. Simeprevir, ASV, and paritaprevir are primarily metabolized by the liver and hence may accumulate in patients with advanced liver failure.

The mean steady-state area under the receiver operating characteristic curve (AUC) of simeprevir was 2.4- and 5.2-fold higher than in HCV uninfected healthy subjects in cirrhotic patients with moderate hepatic impairment (CPS:B) or with severe hepatic impairment (CPS:C), respectively [44]. In patients with severe hepatic impairment, paritaprevir, ritonavir, and dasabuvir AUC values increased by 945%, 13%, and 325%, respectively, compared to subjects with normal liver function. Ombitasvir AUC values decreased by 54% in subjects with severe hepatic impairment [45]. In the absence of data, therefore, simeprevir and the 3D combination are not recommended for use in patients with severe hepatic impairment (CPS:C). In contrast, NS5A inhibitors needed no dose adjustment in this population (PK data of DAAs are summarized in Table 4).

Discussion

The advent of potent and save direct-acting antivirals (DAAs) has revolutionized treatment of chronic hepatitis C virus infection, enabling us to treat almost each patient with interferon-free all-oral regimens. This therapeutic advance may have the greatest impact in patients awaiting transplantation or liver transplant recipients with HCV recurrence (Fig. 1). The broadened armamentarium of combination therapies with DAAs may also allow for more individualized strategies, but solid data are missing at present. So far, five studies using all-oral IFN-free regimens within the post-transplant setting have been published [32,38–40,42], including a total of 287 patients. In particular, data on safety and treatment duration are missing. Patients with severe kidney impairment (creatinine clearance <30 ml/min) may require lowering of the dose of SOF, as its active metabolite is renally excreted.

In patients with limited hepatic functional capacity, elimination of simeprevir, paritaprevir, and dasabuvir is decreased and may lead to adverse effects.

Nevertheless, drug–drug interactions might be still a matter of concern especially when protease inhibitors are used. As there are numerous drug–drug interactions (DDIs) to come up in daily clinical routine, physicians should use Web-based platforms before treatment initiation with DAAs or if additional drug treatment is needed (http://hep-druginteractions.org).

The role of RBV co-administration within an all-oral IFN-free DAA-regimen in this difficult to treat population is still open. An addition of RBV may allow for shorter treatment duration without losing efficacy at cost of worse tolerability.

As data obtained in prospective phase-II and phase-III studies may not be translated into the real-world setting [46], upcoming real-life data will further broaden our understanding to individualize treatment strategies in patients within the transplant setting.

Table 3. Published-/Interim Data of all-oral IFN-free regimens – post-transplant setting.

DAA regimen	Trial name	Cohort	TX duration (weeks)	Enrollment	HCV-GT	otR WE4	SVR12
A: Published Data							
Phase II (published)							
3D + RBV	Kwo *et al.* [42] – *CORAL-1* prospective, multicenter, open-label (EU/USA)	Naïve/experienced; 12 months post-OLT; no cirrhosis	24	34/100%	ns (GT1a: 85%)	34/100 LLOQ	33/97% LOQ
SOF + RBV	Charlton *et al.* ([38], international) Prospective, multicenter, open-label	Naïve/experienced (88%); post-OLT; CPS:A (40%)	24	40/100%	1–4 (1a:55%)	40/100 LLOQ	28/70%
SOF + RBV (±IFN)	Forns *et al.* [39] compassionate use (USA)	ns; post-transplant early (incl. FCH) & chronic recurrence (compensated/ decompensated cirrhosis)	24–48	104/100% Early: 52/50% Chronic: 52/50%	1–4 (1a:35%)	56/54% LLOQ 24/46% 33/65%	54/59% 35/73% 19/43%
SOF + SMV (+RBV in 24/1%)	Pungpapong *et al.* [40] multicenter (USA)	Naive/experienced (IFN-dual; IFN-triple; IFN + SOF); HCV recurrence/ FCH (11%)	12	109/100%	1 (1a:62%)	TnD: +RBV:46% -RBV: 53%	60/91%
B: Interim Data							
AASLD 2014 (preliminary)							
SOF/LDV FDC + RBV	Reddy *et al.* [43] – *SOLAR-1* prospective, multicenter (USA)	Naive/experienced (83%); HCV recurrence (compensated/ decompensated)	12 vs. 24	F0–F3: 111 CPS:A: 51/23.3% CPS:B: 52/22.9% CPS:C: 9/4.0%	1 + 4	ns	12 wes:53/96%; 24 wes: 55/98% 12 wes: 25/96%; 24 wes: 24/96% 12 wes: 22/85%; 24 wes: 15/83% 12 wes: 3/60%; 24 wes: 2/67%
SOF-based/diverse	Brown *et al.* [56] – *HCV-TARGET (EU/USA)* longitudinal, observational, multicenter	Naive/experienced (57–6,6% PI-failures); HCV recurrence; cirrhosis (56%)	ns	227/100% (245 consented) SOF + PR: 27/12% SOF + RBV: 57/25% SOF + SMV: 111/49% SOF + SMV + RBV: 32/14%	1: 179/79%; 2: 20/9%; 3:19/8%; ns: 9/4% 1:13.4%; 2: 0%; 3:5.3% 1: 7.3%; 2: 100%; 3: 94.7% 1: 61.8%; 2: 0%; 3: 0% 1: 17.9%	ns	61/90%

Table 3. continued

DAA regimen	Trial name	Cohort	TX duration (weeks)	Enrollment	HCV-GT	otR WE4	SVR12
SOF-based/diverse	Leroy *et al.* [57] – *ANRS CO23 CUPILT*	FCH	24	21/100% SOF + PR:2/9.5% SOF + RBV:6/28.6% SOF + DCV: 1/4.8% SOF + DCV + RBV:12/57%	1:76%;3:10%;4:14%	14% TnD	SOF + DCV ± RBV 12 wes: 15/100%
SOF + DCV	Conti *et al.* [58], EU	Recurrent HCV	Up to 24	55/100%	1a:29%;1b:33%;1 g:2%; 2:11%;3:15%;4:11%	EVR: 50%	
SOF-based/diverse	Jensen *et al.* [59] – *HCV-TARGET 2.0* longitudinal, observational (EU/USA)	Naive/experienced; post-OLT	ns	70/100%–227/100%	1–3	ns	Abst.: 61/87%; AASLD: ns
SOF-based/diverse	Satoskar *et al.* [60] multicenter (USA)	HCV recurrence	ns	59/100% SOF + PR:8/13.5% SOF + SMV:19/32% SOF + SMV + RBV:6/10% SOF + RBV:26/44%	1 ns ns ns ns	67% TnD 63% TnD 50% TnD 43% TnD	
SOF + DCV ± RBV	Bzowej *et al.* [61], (USA)	ns; severe HCV recurrence/FCH	24	6/100%	1a	2/33% LLOQ* 3/50%: 24–216 IU/ml 1 not yet	
SOF + SMV ± RBV	Gordon *et al.* ([62], USA)	ns; post-OLT	12	17/100%	1	ns	13/81%
SOF + SMV	Gutierrez *et al.* ([63], USA)	ns; post-OLT	12	32/100%	1 (1a:55%)	47% TnD	
SOF + SMV	Suliman *et al.* ([64], USA)	Naive/experienced	12	10/100%	1a	10/100% TnD	
SOF + SMV + RBV	Nair *et al.* ([65], USA)	Naive/experienced (IFN-dual); severe HCV recurrence	12	22/100%	1 (1a:86%)	22/100% TnD	
SOF + SMV ± RBV	Ripper *et al.* ([66], USA)	Naive/experienced; HCV recurrence	12	25/100%	1 (1a:60%)	14/61% LLOQ*	
SOF + SMV	Punzalan *et al.* ([67], USA)	Naive/experienced (41% pre/post-OLT-NR); HCV recurrence	12	27/100%	1	24/92% – LLOQ*	22/100%
DAC + SMV + RBV	Papadopoulos-Köhn *et al.* ([68], EU)	HCV recurrence	24	6/100%	1 (1a:17%)	ns	
SOF + SMV ± RBV	Crittenden *et al.* ([69], USA)	Naive/experienced (89%/IFN-dual); HCV recurrence	12	35/100%	1 (1a:74%)	27/87% TnD	16/89%

Table 3. continued

DAA regimen	Trial name	Cohort	TX duration (weeks)	Enrollment	HCV-GT	otR WE4	SVR12
SOF/SMV; SOF/RBV	Yaseen Alsabbagh *et al.* ([70], USA)	Naive/experienced [IFN-dual/PI-based triple (BOC/TPV)]; HCV recurrence	12	11/65% SOF/SMV 6/35% SOF/RBV	1 1/3	11/100% TnD 6/100% TnD	
SOF + SMV ± RBV	Ford *et al.* ([71], US)	Naive/experienced (54%); HCV recurrence	12	37/100%	1 (1a:68%)	17/46% – TnD	34/92%
SOF-based (+DCV/SMV/RBV)	Kozbial *et al.* [72] retrospective, multicenter (AUT/EU)	Naïve/experienced; HCV recurrence	24	29/100%	1,3,4	7/25% TnD	5/33%
SOF + SMV	O´Dell *et al.* ([73], US)	HCV recurrence severe HCV recurrence/FCH	12	16 28	1	12/75% TnD	
SOF-based/diverse	Andreone *et al.* [74] – AISF-SOFOLT compassionate use (ITALY/EU)	ns; ESLD/FCH	ns	69/100% SOF + RBV:52/75% SOF + PR:13/19% SOF + DCV:3/4% SOF + SMP + RBV:1/1%	1–4	ns	27/73% 16/64% 8/89% 3/100% ns
SOF versus historically pegIFN ± RBV/IFN-triple (BOC/TPV)	Seifert *et al.* ([75], GER/EU)	ns; post OLT	 24 ns	35/100% SOF-based:18/51% IFN-based:17/49%	ns	 8/62% TnD 4/24% TnD	ns
DCV-based/diverse	Fontana *et al.* ([76], EU/US)	Naive/experienced (67%); severe HCV recurrence (FCH:57%; cirrhosis: 30%)	up to 24	106/30%	1	ns	SOF + DCV: 9/75%
SMV + DCV versus SMV + SOF	Londoño *et al.* [77] compassionate use (EU)	Severe HCV recurrence/FCH	ns	28/100% SMV + DCV + RBV:16/57% SMV + SOF + RBV:12/43%	1 or 4 (1b:98%)	13/50% TnD	7/70%

*<25 IU/ml.

A + B: HCV GT: HCV genotype; otR: on-treatment response; WE: week; EoT: end of treatment; SVR: sustained virological response; IS-regimen: immunosuppressive; 3D: paritaprevir/r + ombitasvir + dasabuvir; RBV: ribavirin; SOF/LDV FDC: sofosbuvir + ledipasvir fixed dose combination (Harvoni®, Gilead); DCV: daclatasvir (Daklinza®; Bristol-Myers Squibb); SMV: simeprevir (Olysio®; Janssen-Cilag); BOC: boceprevir (Victrelis®; MSD); TPV: telaprevir (Incivo®/Incivek®; Janssen-Cilag); CPS: Child–Pugh score; FCH: fulminant cholestatic hepatitis; HCV: hepatitis C; IFN: interferon; OLT: liver transplantation; ESLD: end-stage liver disease; LLOQ: lower limit of quantitation; we: weeks; BT: breakthrough; TnD: target not detected; EVR: early virological response; ns: not specified; TAC: tacrolimus; CSA: cyclosporin; SIR: sirolimus; DAA: direct-acting antivirals; HD: hemodialysis.

Table 4. Dose adjustments according to pharmacokinetic data.

	Child–Pugh Score		
Component	A (5–6 points)	B (7–9 points)	C (≥10 points)
NS3/4A – protease inhibitors			
Asunaprevir	AUC × −0.79 – no dose adjustment	AUC × 9.8 – avoid use	AUC × 32 – use not recommended
MK-5172	No dose adjustment	No dose adjustment	No PK data available
Paritaprevir/r	AUC × −0.71 – no dose adjustment	AUC × 1.62 – no dose adjustment	AUC × 10.23 – use not recommended
Simeprevir [33]	No dose adjustment	AUC × 2.44 – no dose adjustment	AUC × 5.22 – use not recommended
NS5A – polymerase inhibitors			
Daclatasvir	AUC × −0.57 – no dose adjustment	AUC × −0.62 – no dose adjustment	AUC × −0.64 – no dose adjustment
Ledipasvir	No dose adjustment	No dose adjustment	No dose adjustment
MK-8742	No dose adjustment	No dose adjustment	No PK data available
Ombitasvir	AUC × 0.92 – no dose adjustment	AUC × 0.70 – no dose adjustment	AUC × 0.45 – no dose adjustment
NS5B – polymerase inhibitors			
Dasabuvir	AUC × 1.17 – no dose adjustment	AUC × 0.84 – no dose adjustment	AUC × 4.19 – use not recommended
Sofosbuvir	No dose adjustment	AUC × 1.26 – no dose adjustment	AUC × 1.4 – no dose adjustment

AUC: area under the receiver operating curve; PK: pharmacokinetic; MK-8742 (Elbasvir®; Merck); modified from: Coilly *et al.* [79], Ouwerkerk-Mahadevan *et al.* [43], Khatri *et al.* [44], Gambato *et al.* [10].

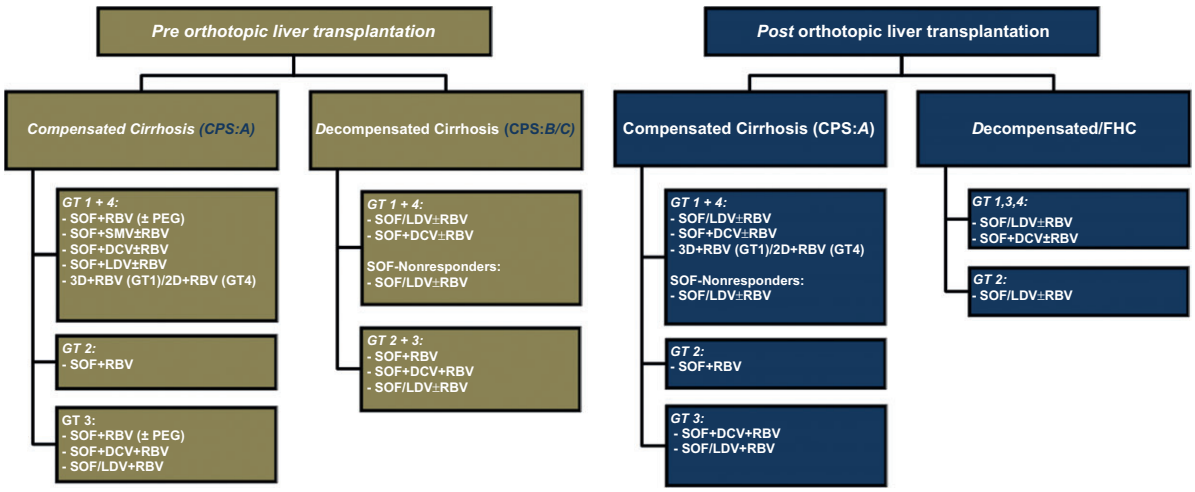

Figure 1 Recommended Regimens in the pre- and post-transplant setting. Treatment duration according to regimen; OLT: orthotopic liver transplantation; CPS: Child–Pugh score; SOF: sofosbuvir (Sovaldi®; Gilead); SMV: simeprevir (Olysio®; Janssen-Cilag); DCV: daclatasvir (Daklinza®; Bristol-Myers Squibb); SOF + LDV: sofosbuvir + ledipasvir (Harvoni®; Gilead); 3D: paritaprevir/r + ombitasvir (Viekira Pak®/Viekirax®) *plus* dasabuvir (Exviera®; AbbVie); 2D: paritaprevir/r + ombitasvir (Viekira Pak®/Viekirax®; AbbVie); NR: nonresponse; RBV: ribavirin; GT: genotype; PEG: pegylated interferon-alpha2; modified from AASLD Recommendations for testing, managing, and treating hepatitis C. December 2014 [27]; http://www.hcvguidelines.org.

The optimal timing of treatment initiation in patients listed for transplantation should be addressed by further studies. HCV eradication before OLT improves graft survival rates as well as overall survival rates in the long run, but may also improve liver function to a degree that the patient can be delisted [47]. Starting treatment before transplantation seems to be an ideal concept and is feasible in patients with HCC listed for OLT. Patients with expected time till transplantation of <2 months may be better treated after successful transplantation, as HCV recurrence rate is about 60% in the peritransplant setting [32].

The main hurdle in future is whether patients get access to these effective but also expensive therapies. Even in first world countries, the economic pressure limits the number of patients who could receive PR-free regimens. Within each country, diverse insurance and reimbursement systems necessitate an individualized approach, but dealing with health-care policies and different reimbursement strategies is not to be answered by physicians.

Nevertheless, the use of IFN-free treatment regimens in OLT patients is strongly advised by recent AASLD and EASL recommendations [15,16].

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