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TOPIC HIGHLIGHT

2015 Advances in Hepatitis C virus

Impact of new treatment options for hepatitis C virus infection in liver transplantation

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Abstract

Liver transplant candidates and recipients with hepatitis C virus (HCV)-related liver disease greatly benefit from an effective antiviral therapy. The achievement of a sustained virological response before transplantation can prevent the recurrence of post-transplant HCV disease that occurs universally and correlates with enhanced progression to graft cirrhosis. Previous standard-of-care regimens (*e.g.*, pegylated-interferon plus ribavirin with or without first generation protease inhibitors, boceprevir and telaprevir) displayed suboptimal results and poor tolerance in liver transplant recipients. A new class of potent direct-acting antiviral agents (DAA) characterized by all-oral regimens with minimal side effects has been approved and included in the recent guidelines for the treatment of liver transplant recipients with recurrent HCV disease. Association of sofosbuvir with ribavirin and/or ledipasvir is recommended in liver transplant recipients and patients with decompensated cirrhosis. Other regimens include simeprevir, daclatasvir, and combination of other DAA. Possible interactions should be monitored, especially in coinfected human immunodeficiency virus/HCV patients receiving antiretrovirals.

Key words: Hepatitis C virus; Direct antiviral agents; Liver transplantation

Core tip: Until recently, a well-tolerated and effective treatment protocol to address the recurrence of hepatitis C virus (HCV) infection following liver transplantation has been an important unmet clinical need. Safe and effective treatment options are now available thanks to the approval of new classes of direct antiviral agents. The aim of this review was to summarize the outcome of previous treatments and discuss the impact of current options for the treatment of HCV among liver transplantation candidates and recipients, including coinfected human immunodeficiency virus/HCV patients.

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INTRODUCTION

An estimated 130 to 170 million people are infected with hepatitis C virus (HCV) worldwide, and an additional 3 to 4 million are newly infected each year[1]. The epidemiology and burden of HCV infection vary geographically, with prevalence rates ranging from < 1% to > 10%[2]. Overall, around 25% of all cases of cirrhosis and HCC are related to HCV, with significantly higher rates among countries that have a high prevalence of the disease[3]. Chronic HCV infection is associated with substantial mortality, with over 350000 deaths per year attributed to HCV-related cirrhosis and hepatocellular carcinoma (HCC)[4-6]. The development of cirrhosis and HCC due to HCV infection represents the most common indication for liver transplantation (LT) in the United States, accounting for around 40% of all cases on the United States waiting list[7]. Furthermore, projections have identified a constant increase in the number of patients with HCV-related end-stage liver disease (ESLD) who will be listed for LT over the next 10 years[8,9]. In this patient population, transplantation is an effective treatment to reduce morbidity and mortality. HCV recurrence, however, is universal in liver transplant recipients (LTR). Since HCV disease is associated with accelerated graft loss and diminished patient survival, the availability of a safe and efficacious therapy is essential among LTR[10]. For this group of patients, the real challenge for HCV treatment starts after LT.

In the past, the use of HCV treatments including pegylated interferon (Peg-INF) and ribavirin (RBV), either alone or in association with first generation protease inhibitors (PI) such as telaprevir or boceprevir, was limited by suboptimal viral responses, drug-drug interactions, and the occurrence of severe side effects, some of which have caused graft loss or have been fatal[11]. The approval of highly effective new molecules (*i.e.*, new wave NS3-4A PI, nucleotide analogues, NS5A inhibitors) has revolutionized the scenario for the treatment of HCV infection. Goals of the new anti-HCV drugs include outcome improval, reduction of side effects and drug-drug interactions, and regimen simplification. As summarized in Table 1, newly anti-HCV drugs are expected to optimize the treatment before LT, allowing patients to undergo transplantation with undetectable HCV viral load, and after LT, offering safe and broadly effective options to prevent recurrence of HCV infection.

To keep pace with the newest discoveries in the field of HCV treatment, the Infectious Diseases Society of America (IDSA) and the American Association for the Study of Liver Diseases (AASLD), in collaboration with the International Antiviral Society-United States (IAS-United States), created a website that allows to access updated, evidence-based recommendations for the management of HCV[12].

ANTI-HCV DRUGS: OLDER AND NEWER OPTIONS FOR PATIENTS WITH ADVANCED LIVER DISEASE

The goal of treatment in HCV infected individuals is the achievement of virologic cure (or sustained virological response, SVR), defined as the absence of detectable levels of HCV RNA (*e.g.,* $\leqslant$ 25 IU/mL with an FDA approved nucleic acid test) at least 12 wk after completion of therapy (SVR12). In more than 99% of patients, SVR12 has been shown to be durable for 5 years or more[13]. Successful HCV treatment dramatically decreases hepatic decompensation events, HCC incidence, and liver-related mortality[14]. Furthermore, it has been demonstrated that patients with advanced fibrosis who achieve SVR have a decreased need for LT compared with patients who do not attain SVR[15]. Thus, prompt HCV treatment is prioritized for advanced liver disease, and urgent initiation is advocated in patients with severe extrahepatic HCV disease, significant fibrosis (Metavir F3-F4), decompensated cirrhosis (Child-Turcotte-Pugh B and C), and candidates or recipients of LT[16].

Interferon-ribavirin combination

Until recently, the combination of IFN or Peg-IFN and RBV has been considered the treatment of choice for patients with chronic HCV, including those progressing to cirrhosis. With this regimen, SVR can be achieved in 30%-40% and 70%-90% of patients with HCV genotype 1 *vs* genotypes 2 or 3, respectively[17-19]. Over the past two decades, modest efficacy along with a high incidence of serious adverse events (SAE) have characterized this treatment; furthermore, Peg-INF/RBV optimal timing, dose, and duration in difficult-to-treat populations requiring urgent treatment, such as patients with ESLD, have never been clearly defined.

Boceprevir and telaprevir

In 2011, the first generation of direct-acting antivirals (DAA), boceprevir (BOC) and telaprevir (TVR), was approved for patients with genotype 1 HCV disease. BOC is a keto-amide serine PI that reversibly binds to the HCV nonstructural 3 (NS3) active site; TVR inhibits the NS3/4A HCV protease[20,21]. SVR with PI-based triple therapy (*e.g.,* association of a PI with Peg-IFN/RBV) reached 68%-75% in naïve and 59%-88% in experienced patients[22-25]. Due to the improved rate of SVR attainment for genotype 1 patients, the use of

Table 1 Expected benefits of new treatments for hepatitis C virus infection

Target population	Main objectives	Outcome
General population with chronic HCV infection	Achieve excellent SVR rates for all genotypes, reduce side effects, shorten treatment duration, simplify regimen schedules	Reduced ESLD incidence and indication for LT
Patients on LT waiting list	Achieve pre-transplant undetectable HCV-RNA; improve MELD scores	Reduced post-LT HCV recurrence; improved clinical conditions
Recipients of LT with HCV recurrence	Increase SVR rates, reduce side effects and dropouts, decrease drug-drug interactions, simplify regimen schedules	Increased patients and grafts survival
HIV/HCV-coinfected patients and coinfected LT recipients	Increase SVR rates, reduce side effects and dropouts, decrease drug-drug interactions, simplify regimen schedules	Increased patients and grafts survival

HCV: Hepatitis C virus; SVR: Sustained virological response; ESLD: End stage liver disease; LT: Liver transplant; MELD: Model for end-stage liver disease; HIV: Human immunodeficiency virus.

BOC and TVR was initially included as standard-of-care for HCV infection[26]. However, these drugs still had to be associated with Peg-IFN/RBV and required long treatment duration (24-48 wk), causing an increase in treatment burden and side effects. For these reasons, BOC use is no more recommended and TVR has been removed from the market due to the development of more effective compounds[27,28].

DAA

More recently, clinical trials have shown revolutionary results in the treatment of HCV with the use of new DAA and their combination products, with and without Peg-IFN. Due to elevated SVR, good safety profiles, and once to twice daily administration, these compounds have now been incorporated into the AASLD/IDSA recommendations[12].

In December 2013, the United States Food and Drug Administration (FDA) approved sofosbuvir (SOF), a nucleotide polymerase inhibitor of NS5B targeting HCV-RNA replication[29]. SOF is metabolized in its active form that competes with the uridine triphosphate for incorporation into the growing HCV-RNA by the non-structural protein 5B (NS5B) polymerase, acting as a chain terminator[30]. Since the NS5B active site is highly conserved across HCV genotypes, SOF displays a pan-genotypic efficacy[31]. The administration of SOF 400 mg once daily (OD) for 12 wk has been associated with rapid decrease of HCV-RNA and SVR above 85%, either in combination with Peg-IFN/RBV or with RBV alone as part of an IFN-free regimen[32,33]. Safety data has been promising also in advanced, decompensated cirrhosis showing discontinuation rates below 2% and few SAE[34]. Furthermore, low drug-drug interactions have been observed and no dose adjustments were required in patients with hepatic impairment[35]. Simeprevir (SMV, 150 mg OD), a second wave NS3/4A protease inhibitor, has been approved for use in combination with Peg-IFN/RBV in 2013 and, in November 2014, for the treatment of HCV genotype 1 in combination with SOF. IFN-free regimens containing SMV were also well-tolerated and showed overall SVR12 above 90%[36]. The association of ledipasvir (LDV, 90 mg OD), a NS5A inhibitor, with SOF was approved by the FDA in November 2014 based on the results of large phase 3 multicenter, open-label, randomized clinical trials showing SVR between 93% and 99%[37,38]. A four-drug, twice daily combination regimen, consisting of 75 mg of paritaprevir (a NS3/4A protease inhibitor), 50 mg of ritonavir (a CYP3A inhibitor, used as a pharmacologic booster), and 12.5 mg of ombitasvir (a NS5A inhibitor), packaged with two 250 mg dasabuvir (a non-nucleoside NS5B polymerase inhibitor) tablets has also been approved by the FDA and studied in combination with RBV for genotype 1 patients[39-41]. Daclatasvir (DCV, 60 mg OD), a pan-genotypic NS5A inhibitor, was approved in Europe in August 2014 and is currently used in combination with other DAA in various countries[16].

DAA therapy in patients with cirrhosis

Although characterized by ground-breaking results, recent trials have underrepresented the populations traditionally associated with poorer treatment outcomes, including patients with advanced liver fibrosis. Nevertheless, encouraging results seem to emerge from reports comprising "real world" data collected from several institutions. Table 2 summarizes the outcome of the most representative clinical trials including cirrhotic patients treated with DAA.

SVR > 50% have been reported among cirrhotic patients treated with SOF/RBV although, in genotype 3 patients receiving 12-wk regimens, cirrhosis was associated with limited responses[33,42]. LDV/SOF, with or without RBV (± RBV), has shown excellent SVR and low adverse effects in patients with cirrhosis[43,44]. A post-hoc analysis of data from seven clinical trials including 513 patients with genotype 1 HCV and compensated cirrhosis receiving LDV/SOF for 12 or 24 wk ± RBV showed SVR12 of 98% and 95% for treatment-naïve and previously treated patients, respectively. Results were similar in patients receiving RBV compared to RBV-free regimens, except among previously treated patients who showed the lowest SVR (90%) in the arm without RBV. SAE and discontinuation rates were in the range of 1%-2%[45]. Recently, the results of SOF/SMV ± RBV regimens in a heterogeneous cohort of 995 patients including

Table 2 Sustained virological response among recent clinical trials of new treatment regimens for hepatitis C virus including patients with cirrhosis

Ref.	Trial	Population	Drug	Overall SVR12	SVR12 in cirrhosis
Jacobson *et al*[143], 2014	Fusion	G2, G3 experienced 34% cirrhotic	SOF/RBV 12 *vs* 16 wk	G2 86% *vs* 94% G3 62% *vs* 30%	G2 60% *vs* 78% G3 19% *vs* 61%
Lawitz *et al*[33], 2015	Fission	G2, G3 naïve 20% cirrhosis	SOF/RBV 12 wk *vs* Peg-IFN/RBV 24 wk	G2 97% *vs* 78% G3 56% *vs* 63%	G2 92% *vs* 62% G3 30% *vs* 34%
Jacobson *et al*[143], 2014	Positron	G2, G3 naïve and experienced IFN ineligible	SOF/RBV	G2 93%, G3 61%	G2 92%, G3 21%
Zeuzem *et al*[144], 2014	Valence	G3 extended 24 wk 21% cirrhosis	SOF/RBV	G2 94%, G3 91%	G2 82%, G3 68%
Lawitz *et al*[42], 2015	Lonestar-2	G 2 and 3	SOF/RBV/Peg-IFN	G2 96%, G3 83%	G2 93%, G3 83%
Bourliere *et al*[43], 2015	Sirius	G1 with compensated cirrhosis, NR previous treatment	SOF/LDV 24 wk *vs* SOF/LDV/RBV 12 wk	N/A	97% *vs* 96%
Lawitz *et al*[36], 2014	Cosmos	G1 NR, 52% F3-F4	SOF/SMV ± RBV 12 or 24 wk	92%	94%
Gane *et al*[114], 2014	Electron Ⅱ	G1 naïve, experienced and decompensated, G3 naïve, 15% cirrhosis	LDV/RBV 12 wk	G1 100%, G3 64%	G1 65%

Peg-IFN: Pegylated interferon; RBV: Ribavirin; SVR12: Sustained virological response; G: Genotype; LDV: Ledipasvir; SOF: Sofosbuvir; SMV: Simeprevir; NR: Non responder.

30% of patients with cirrhosis were compared with SOF/PEG/RBV and SOF/RBV[46]. In the group of patients with genotype 1 and previously treated for HCV, a significant difference in SVR was noted between patients without cirrhosis *vs* patients with cirrhosis, with better results for SOF/SIM ± RBV (84% *vs* 65%, respectively) compared to SOF/Peg-IFN/RBV (94% *vs* 80%, respectively). Overall, discontinuation rates around 5% were noted. Other promising DAA combinations include grazoprevir (MK-5172) and elbasvir (MK-8742), showing high SVR12 at 12 wk among patients with genotype 1 and cirrhosis with and without RBV (90% and 97%, respectively)[47]. MK-5172/MK-8742 combination has recently also been tested among patients with advanced chronic kidney disease, showing SVR12 of 99%[48]. The 3DAA combination of DCV with asunaprevir (NS3 protease inhibitor) and BMS-791325 (non-nucleoside NS5B inhibitor) was studied in patients with HCV genotype 1 infection and compensated cirrhosis. SVR were 87% and 93% in experienced patients treated with and without RBV, respectively[49].

IMPACT OF RECURRENT HCV INFECTION AFTER LIVER TRANSPLANTATION

Patients showing detectable HCV-RNA levels at transplantation universally experience recurrent postoperative HCV infection[50]. Reinfection likely occurs during graft reperfusion *via* circulating virions or infected mononuclear cells, and it is documented as detection of HCV-RNA in serum or in the allograft itself. HCV-RNA can be present as early as 48 h post-LT, with expression of HCV antigens on the hepatocytes from postoperative day 10[51-53]. Post-transplant HCV kinetics has shown that serum HCV-RNA levels reach pre-LT titers usually within day 4, then increase and peak around month 3, attaining levels 10- to 100-fold greater than the mean pre-LT months around one year after LT[54]. Histologic progression of HCV during immunosuppressive therapy is more rapid than that in nontransplant patients, probably due to a compromised virus-specific T-helper subtype 1 (TH1) CD4 immune response[55]. Liver biopsies are currently the most effective method to diagnose and differentiate HCV disease, showing good sensitivity starting from 3 mo after LT[51]. In earlier stages, histological differentiation between HCV disease, reperfusion injury, and rejection can be challenging. A small proportion of patients (4%-7%) develop fibrosing cholestatic hepatitis (FCH), an accelerated course of liver injury associated with very high levels of viremia, rapid allograft failure, and poor response to therapy due to direct cytotoxic damage favored by a lack of specific anti-HCV response along with increased TH2 cytokine expression[56]. Following graft infection, chronic HCV disease develops in 75% to 90% of patients. Evolution towards cirrhosis is reported 5% to 30% of cases within 5 years and up to 40% within 10 years compared to 20 years in the nontransplantation setting[57-59]. HCV-associated graft failure represents the most common cause of graft loss and patient mortality in HCV-infected recipients, occurring in approximately 10% of LT recipients within 5 years[60]. Overall, survival of patients and grafts with recurrent post-LT HCV infection is lower compared to patients receiving LT for other indications[57,61]. Various risk factors have been associated with unfavorable outcomes in HCV-infected recipients. Some of them, such as prolonged cold ischemia time, advanced donor age, CMV hepatitis, treatment for acute rejection (*e.g.*, steroid bolus or monoclonal antibody OKT3), development of postoperative insulin resistance diabetes mellitus or metabolic syndrome are potentially modifiable and should be either carefully evaluated in the process of donor selection or monitored in the post-LT[10,62-64].

Table 3 Pros and cons of hepatitis C virus treatment before and after liver transplant

	Before LT	After LT
Aim	Prevention of HCV recurrence	Treatment of HCV recurrence
Advantages	Undetectable HCV-RNA at transplantation correlates with low rates of post-LT HCV recurrence	Increased tolerance to treatment
Disadvantages	Low eligibility due to compromised baseline conditions High rates of serious side effects and discontinuation rates Low SVR rates	High rates of adverse effects Moderate SVR rates Drug-drug interactions

HCV: Hepatitis C virus; LT: Liver transplant; SVR: Sustained virological response.

Other risk factors include high preoperative model for end-stage liver disease (MELD) score, fibrosis stage ⩾ 2 at 12-mo biopsy, recipient IL28B TT genotype, and history of HCC[10,50,65-68]. Marked, transient hyperbilirubinemia has been associated with allograft cirrhosis in HCV-infected LT recipients[69]. Among virological factors, high pretransplantation HCV-RNA titers (> 1 mEq/mL) have been strongly related with severe recurrent HCV. Patients with lower pretransplantation HCV RNA had 5-year survival of 84% compared to 57% of patients with higher HCV RNA titer ($P < 0.0001$)[70]. Interestingly, neither viral genotype nor elevated post-LT viral titers have been found to be reliable predictors of outcome. At best, the most effective way to prevent HCV recurrence is the eradication of HCV prior to LT.

ANTIVIRAL THERAPY IN RECURRENT HCV INFECTION

HCV infection treatment: Before or after liver transplantation?

The likelihood of SVR diminishes with increasing severity of liver disease. In patients with cirrhosis, SVR rates are reduced compared to non-cirrhotic patients, ranging between 40%-50% for Child-Turcotte-Pugh (CTP) class A and being as low as 7%-26% for CTP class C patients treated with Peg-IFN/RBV[17-19,71]. Genotype 1 and 4 patients with cirrhosis showed lower treatment responses compared with genotype 2 and 3 patients (33% *vs* 57%, respectively)[71]. Factors such as poor tolerability, dose reductions, and therapy discontinuation have a significant impact on therapy outcomes in this patient population[72]. IFN-based treatment is generally poorly tolerated and can be associated with severe infections and liver decompensation; overall, up to a third of patients is reported to discontinue the treatment because of adverse events[72]. Nevertheless, the evidence that high HCV-RNA levels at transplantation correlate with rapid, clinically evident recurrence of post-transplantation HCV disease supports the attempt of an aggressive pre-transplantation treatment[10]. IFN is contraindicated in patients with decompensated cirrhosis; selected patients listed for LT showing compensated or mildly decompensated liver disease, however, have been previously considered for treatment with Peg-IFN/RBV ± TPV or BOC. A significant portion of LT candidate often present advanced ESLD or absolute contraindications to IFN-based therapy, requiring to delay HCV treatment after transplant. With the recent introduction of new DAA, successful treatment of patients on transplant waiting list seems possible. In this group, a reduction in MELD score caused by the positive impact of the treatment on liver decompensation can potentially lead to patient delisting, therefore lowering the proportion of waiting list registrants for transplantation due to HCV-related ESLD.

Post-LT treatment is generally started following the 12-mo liver biopsy if histologic severity reaches grade 3 or 4 inflammation or stage 2 or higher of fibrosis. Irrespective of grade and stage, cholestatic hepatitis is usually an indication for treatment[10]. Treatment of post-LT recurrent HCV disease is limited by moderate SVR, potential drug-drug interactions, and toxicity. In this cohort, as in the pre-transplant group, new anti-HCV therapies can provide substantial improvements in terms of efficacy and safety. Aims, advantages and disadvantages of the pre-LT and post-LT approaches are reported in Table 3.

Treatment before liver transplantation

The treatment of patients with decompensated cirrhosis is problematic due to coexisting leukopenia, thrombocytopenia, and other manifestations of ESLD that cause poor drug tolerance, often requiring the use of grow factors and transfusions[73]. In the registration trials for Peg-IFN/RBV, SVR rates were 5% to 15% lower in patients with advanced fibrosis or cirrhosis compared to patients who did not present advanced liver disease[17,18]. Various non-randomized studies have investigated the efficacy of diverse IFN or Peg-IFN-based regimens in HCV-infected patients candidate to LT (Table 4). A study using increasing doses of IFN and RBV based on tolerability demonstrated SVR only in 13% of patients with HCV genotype 1. Predictors of SVR were non-1 genotype, CTP class A for patients with genotype 1, and ability to tolerate full dose and treatment completion[74]. Other reports showed rates of HCV-RNA suppression in patients with advanced liver disease around 20%-30%[75-78]. More recently, Everson *et al*[79] conducted a randomized, controlled trial to test the efficacy and safety of Peg-IFN/RBV, both escalated as tolerated, to prevent post-transplant

Table 4 Outcome of pre-transplant hepatitis C virus therapy in studies with different regimens

Ref.	Population	*n*	Treatment regimen	Outcome	Adverse effects
Everson *et al*[74], 2005	63% decompensated cirrhosis (MELD 11 ± 3.7)	124	IFN (5 MU 3/wk) or Peg-IFN (0.75 μg/kg per week)/RBV (600 mg/d escalated)	SVR 13% (G1), 50% (other genotypes) 53% relapse 29% completed course	13% discontinuations and SAE (2 deaths)
Crippin *et al*[75], 2002	LT waiting list	15	IFN (3 MU 3/wk or 1 MU/d) ± RBV 400 bid	SVR 33%	1.3 SAE/patient (one death)
Forns *et al*[145], 2003	LT waiting list	30	IFN (3 MU/d)/RBV 800 mg/d	SVR 20% (3 relapse after LT)	63% dose reduction
Thomas *et al*[76], 2003	LT waiting list	21	IFN (5 MU/d)	SVR 20% (8 relapse after LT)	No SAE
Carrión *et al*[78], 2009	LT waiting list	51	Peg-IFN/RBV	SVR 20%	39% bacterial infections
Everson *et al*[79], 2013	LT waiting list	59	Peg-IFN/RBV (from 0.75 μg/kg per week and 600 mg/d escalated)	SVR12 22% (G 1-4), 29% (G 2-3), 50% if > 16 wk	68% (2.7 SAE/patient)
Verna *et al*[11], 2015	LT waiting list	29	PI-based triple therapy (93% TVR, 7% BOC)	SVR 52%	31% SAE; one death 28% hospitalizations
Curry *et al*[81], 2015	LT waiting list for HCC (CTP < 7)	43	Sofosbuvir 400/d plus RBV 1000-1200 up to 48 wk	SVR pre-LT maintained in 69% LT	18% SAE 2 discontinuation
Charlton *et al*[82], 2015	Decompensated cirrhosis	108	LDV/SOF/RBV (600 mg/d escalating) 12 *vs* 24 wk	SVR 87% *vs* 89%, CTP B 87% *vs* 89%, CTP C 86% *vs* 87%	26% SAE 3 discontinuation
Poordad *et al*[85], 2015	Advanced cirrhosis (70% CTP B-C)	60	DCV/SOF/RBV 12 wk	SVR 83%, CTP A 91%, CTP B 92%, CTP C 50%	No SAE

LT: Liver transplant; HCC: Hepatocellular carcinoma; CTP: Child-Turcotte-Pugh; IFN: Interferon; Peg-IFN: Pegylated interferon; RBV: Ribavirin; SVR: Sustained virological response; G: Genotype; SAE: Serious adverse effects; MELD: Model for End-Stage Liver Disease; PI: Protease inhibitor; TVR: Telaprevir; BOC: Boceprevir; LDV: Ledipasvir; SOF: Sofosbuvir; DCV: Daclatasvir.

HCV recurrence in patients listed for LT. Overall, 22% of patients with genotype 1, 4 or 6 and 29% of patients with genotype 2 or 3 obtained SVR12. Among patients completing at least 16 wk of treatment, SVR rates reached 50%. In conclusion, IFN-based regimens obtained poor SVR among patients listed for LT, mainly due to an intrinsic reduced response along with a low rate of treatment completion. DAA triple therapy showed increased SVR in a study including 29 patients with low MELD scores but high rates (66%) of prior non-responders. The majority of patients were treated with Peg-IFN/RBV/TVR. Patients on waiting list had SVR of 41% and patients undergoing LT showed SVR of 67%. Despite demonstrating considerably higher SVR rates compared to Peg-IFN/RBV, the use of BOC or TPV was associated with increased SAE and a high pill burden[11]. As shown in Table 4, encouraging results have been displayed by IFN-free HCV regimens. Osinusi *et al*[80] administered SOF in combination with either weight-based (*n* = 24) or low-dose (600 mg daily) RBV for 24 wk to 28 genotype 1 patients, including those with advanced fibrosis. SOF/RBV combination resulted in 50% and 29% SVR in weight-based and low-dose RBV groups, respectively (difference not significant). Advanced liver fibrosis and high HCV RNA at baseline were identified as predictors of relapse. Neither discontinuation nor SAE were registered. SOF/RBV combination was also used in a phase 2 study to treat 61 patients (73% with genotype 1 and 75% previously treated for HCV) waitlisted to undergo LT for HCC. Overall, 49% of treated patients has post-LT SVR; among those who had undetectable HCV-RNA at transplantation, 70% achieve SVR[81]. A number of days of undetectable HCV RNA level pretransplant > 30 was significantly associated with SVR12.

IFN-free, DAA combination therapies have shown the highest rates of SVR among patients with advanced liver disease previously treated for HCV. Cure rates close to 90% in patients with decompensated cirrhosis were reported among 108 patients receiving LDV/SOF/RBV for 12 or 24 wk[82]. Of note, a substantial improvement of liver synthesis function of the patients with successful HCV therapy was documented by an improvement in MELD score. Nevertheless, despite achieving SVR, liver disease continued to progress in some patients. Although no current data is available in patients with decompensated cirrhosis treated with LDV/SOF without RBV, promising results have been achieved in patients with compensated cirrhosis, including those previously treated with SOF[83,84].

Various IFN-free, DAA combination trials are currently ongoing in patients with decompensated cirrhosis[85,86]. A recent trial included patients with advanced cirrhosis and post-liver transplant HCV recurrence treated with DCV/SOF/RBV for 12 wk. In the cirrhosis cohort, genotype 1 patients achieved overall SVR of 82% (92%, 91% and 50% in CTP A, B, and C, respectively[87].

Current recommendations for the treatment of LT candidates with decompensated cirrhosis include LDV/SOF/RBV for genotype 1 administered for 12 wk

Table 5 Anti-hepatitis C virus therapy in liver transplant recipients with recurrent hepatitis C virus infection: Outcome of main studies from the past 10 years

Ref.	Population	*n*	Treatment regimen	SVR	Adverse effects
Interferon (IFN) or pegylated interferon (Peg-IFN) plus ribavirin (RBV) regimens					
Fernández *et al*[95], 2006	LTR with recurrent HCV	47	Peg-IFN/RBV	23%	21% SAE
Carrión *et al*[77], 2008	LTR with mild recurrence (F0-F2)	27	Peg-IFN/RBV	48%	56% discontinuation
Berenguer *et al*[92], 2008	LTR with recurrent HCV	89	IFN/RBV *vs* Peg-IFN/RBV	16% *vs* 48%	20% decompensation; 15% deaths
Hanouneh *et al*[93], 2008	LTR with recurrent HCV	53	Peg-IFN/RBV	35%	23% SAE
Ueda *et al*[146], 2010	LTR with recurrent HCV (G1)	34	Peg-IFN alfa-2b + RBV	50%	18% discontinuation
DAA triple therapy with Peg-IFN/RBV plus boceprevir (BOC) or telaprevir (TVR)					
Verna *et al*[109], 2015	Advanced fibrosis (F > 3) and 9 FCH	49	Peg-IFN/RBV/TVR or BOC	51% AF 44% CH	22% AF and 33% CH decompensation
Pungpapong *et al*[108], 2013	LTR with recurrent HCV	60	Peg-IFN/RBV/TVR (35) or BOC (25)	67% TVR 45% BOC	12% decompensation, 2 deaths
Coilly *et al*[107], 2014	LTR with recurrent HCV	37	Peg-IFN/RBV/TVR (19) or BOC (18)	20% TVR 71% BOC	14% SAE, 27% infection, 3 deaths
IFN-free DAA regimens					
Forns *et al*[111], 2015	Post-LT decompensated cirrhosis and FCH	92	SOF/RBV ± Peg-IFN 24-48 wk	59%	46% SAE
Charlton *et al*[110], 2015	LTR with recurrent HCV	40	SOF/RBV 24 wk	70%	No SAE
Reddy *et al*[44], 2015	Post LT recurrence (121 CPT B and C)	223	LDV/SOF/RBV 12 *vs* 24 wk	94% (60% CTP C)	4% SAE, 3% discontinuation
Gutierrez *et al*[118], 2015	Post LT recurrence	61	SOF/SMV ± RBV	93%	No SAE
Pungpapong *et al*[119], 2015	Post LT recurrence	123	SOF/SMV ± RBV	90%	1 death possibly related to treatment
Kwo *et al*[103], 2014	Post LT recurrence (G1)	34	Paritaprevir/r/Ombitasvir and Dasabuvir/RBV	97%	1 discontinuation
Poordad *et al*[85], 2015	Post LT recurrence	53	DCV/SOF/RBV 12 wk	94%	1 discontinuation (SVR); no SAE

LTR: Liver transplant recipients; SVR: Sustained virological response; CTP: Child-Turcotte-Pugh; SAE: Serious adverse event; FCH: Fibrosing cholestatic hepatitis; SOF: Sofosbuvir; SMV: Simeprevir; LDV: Ledipasvir; r: Ritonavir; DCV: Daclatasvir.

(or 24 wk if RBV intolerant or previous SOF therapy), SOF/RBV for 48 wk in genotypes 2 and 3 and DCV/SOF/RBV for 12 wk for all genotypes[16,85].

HCV treatment after LT

The achievement of SVR in recurrent HCV infection after LT is associated with stabilization of fibrosis and improved graft survival. In this setting, however, poor therapy tolerability represents an important limitation. Some studies have explored the effects of early or pre-emptive treatment, starting anti-HCV therapy immediately after LT in patients who may tolerate it, such as HCC patients with low MELD[88]. The rationale for this approach is to act at a time when HCV-RNA is low and histologic damage is virtually absent[89]. Among living donor recipients, in particular, the treatment could be easily planned and has shown encouraging results[88]. Overall, the success of this strategy was limited by low SVR and high rates of discontinuation, while the effective impact on patients' survival has not been clearly proven[90,91]. In the treatment of clinically evident disease, non-controlled studies including patients with recurrent HCV infection showed SVR rates ranging from 26% to 50% for Peg-IFN/RBV therapy (Table 5)[92-101]. When initiated at the early stages of HCV recurrence (F0-F2), an advantage of Peg-IFN/RBV treatment was demonstrated, showing SVR around 50%; however, the possible increased risk of rejection was not defined[77]. Similarly to nontransplant patients, factors associated with SVR among LTR included low pretreatment HCV RNA levels, absence of advanced cirrhosis, having a genotype other than 1, and early virological response[93]. A systematic review encompassing 38 studies showed overall SVR of 24% for standard IFN and 27% for Peg-IFN/RBV, with discontinuation rates of 24% and 26%, respectively[102]. Similarly to LT candidates, PI-based triple therapy in HCV-infected LT recipients was initially deemed as a combination that would have drastically increased the rates of SVR. Nevertheless, this treatment did not meet the expectations, showing suboptimal efficacy counterbalanced by high SAE rates and challenges in managing drug-drug interactions between PI and calcineurin inhibitors (CNI), particularly tacrolimus[103-106]. Overall, anemia, infection rates, and liver decompensation have significantly limited this therapeutic approach in LTR[107-109].

2014 AASLD recommendations

A multicenter study has shown SVR of 70% among 40 LTR with compensated HCV disease treated with SOF/RBV for 24 wk[110]. There were no deaths, graft losses or episodes of liver decompensation among post-liver transplantation patients, and no drug-drug interactions were reported between SOF and immunosuppressive agents. Among 92 patients with

Table 6 American Association for the Study of Liver Diseases 2014 recommendations for therapy in recurrent hepatitis C virus post liver transplant

Rating	Population	CPT B and C	Regimen	Daily Dose
Ⅰ B-recommended	G 1, 4 experienced and naïve	RBV 600 mg, increased as tolerated[1]	LDV/SOF/RBV 12 wk	90 mg/400 mg/weight-based[2]
Ⅰ B-alternative	G 1, 4 naïve, RBV intolerant	Not recommended	LDV/SOF 24 wk	90 mg/400 mg
Ⅰ B-alternative	G1	Not recommended	SOF/SMV ± RBV 12 wk	400 mg + 150 mg ± weight-based[2]
Ⅰ B-alternative	G1	Recommended only for non-cirrhosis	Paritaprevir/r/rombitasvir/dasabuvir + RBV for 24 wk	150 mg/100 mg/25 mg/250 mg bid/weight-based[2]
Ⅱ B-recommended	G2 experienced and naïve	600 mg/d, increased as tolerated[1]	SOF/RBV 24 wk	400 mg/weight-based[2]
Ⅰ B-recommended	G3 experienced and naïve	600 mg, increased as tolerated[1]	SOF/RBV 24 wk	400 mg/weight-based[2]
Ⅲ A Not recommended: Regimens containing PEG-IFN, monotherapy with PEG-IFN, RBV, or a DAA; TVR or BOC-based regimens				

[1]*e.g.*, increased monthly by 200 mg/d; [2]1000 mg < 75 kg, 1200 mg > 75 kg. Recommendations are graded according the level of the evidence and strength of the recommendation. G: Genotype; RBV: Ribavirin; LDV: Ledipasvir; SOF: Sofosbuvir; RBV: Ribavirin; r: Ritonavir; DCV: Daclatasvir; DAA: Direct active antiviral; TVR: Telaprevir; BOC: Boceprevir.

severe HCV disease, including liver decompensation, SOF compassionate use program (in association with RBV ± Peg-IFN) showed SVR12 of 59%; higher SVR (73%) were shown in patients treated for early severe recurrence[111]. Based on these results, combination treatments containing SOF are currently included in the 2014 AASLD recommendations for patients who develop recurrent HCV infection post-LT (Table 6)[112]. DAA combination therapy with LDP/SOF/RBV is indicated for patients with genotype 1 and 4, including those previously treated for HCV and patients with decompensated cirrhosis (with reduced RBV dose). The efficacy of this regimen was assessed in a large, multicenter, randomized controlled trial showing high rates of SVR irrespective of the treatment duration (12 wk *vs* 24 wk) along with improvements in MELD score, albumin and bilirubin[113]. The study included 223 LTR with a wide spectrum of histologic and clinical severity of HCV recurrence. Thirty-seven/44 (84%) CTP B and 5/8 (63%) CTP C patients achieved SVR12, compared to 97% of patients with F0-F2 and compensated cirrhosis. Overall, 8 treatment-related SAE were documented. CTP C patients appeared to have lower SVR compared to the other groups, although the number of patients in this group was limited. Although its importance cannot be ascertained, the addition of RBV could have been responsible for the high SVR12 rates observed. According to the AASLD guidelines, a 24-wk course of LDP/SOF is recommended in LTR that are intolerant or ineligible to receive RBV. Patients with genotype 3 including cirrhotic patients, however, have shown suboptimal responses, especially with 12-wk regimens (Table 2). A 24-wk course of SOF/RBV is recommended in patients with genotype 3 with recurrent post-LT HCV disease (Table 6). Indications on the use of LDP/SOF for genotype 3 LTR are not made due to a lack of data in the post-LT setting and limited data among patients with cirrhosis. Nevertheless, a phase Ⅱ study has reported SVR 12 of 100% for LDP/SOF/RBV compared to 64% for LDP/SOF in a cohort of patients with G3 infection (including 15% cirrhotic), potentially suggesting that LDV could even shorten the treatment duration in this group[114]. A limitation in the use of LDV regards the concomitant use of proton pump inhibitors, that attenuate its absorption by > 90%. Promising results in LTR were also shown with the pan-genotypic combination of DCV/SOF/RBV. Analysis from a small group of 12 LTR showed SVR of 75% along with absence of drug-drug interactions and SAE[115]. A study presented at the 2014 AASLD meeting including patients from the same cohort showed CTP score improvements in 20 patients (from 7.3 to 5.8, $P = 0.004$)[116]. More recently, the results of the phase 3 ALLY-1 trial in LTR treated with DCV/SOF/RBV reported overall SVR of 94% regardless of prior treatment experience[86]. Treatment with DCV/SOF/RBV has been included in the 2015 EASL (European Association for the Study of the Liver) recommendations for the treatment of HCV recurrence, including decompensated cirrhosis, in all genotypes[16].

A multicenter study including 34 LTR with mild genotype 1 HCV recurrence (F0-F2) treated with paritaprevir/ritonavir, ombitasvir, twice-daily dosed dasabuvir, and RBV for 24 wk showed overall SVR of 97%[103,117]. Dose adjustments were needed for cyclosporine and tacrolimus due to interactions between ritonavir and CNI. Only one discontinuation in a patient who achieved SVR was noted. Since the efficacy and tolerability in patients with more advanced HCV infection are not well known, this regimen is currently only recommended for LTR without cirrhosis. The association of SMV/SOF ± RBV is suggested as an alternative regimen in genotype 1 patients without liver decompensation and recurrent HCV disease post-LT. A retrospective analysis of a single center involving 61 patients with HCV genotype 1 infection who received a 12-wk combination regimen of SOF/SMV post-LT showed SVR12 of 93% compared with 67% in patients with advanced fibrosis[118]. No SAE occurred during treatment. Similar results were obtained in a large multicenter study encompassing 123 patients receiving SOF/SMV after a median time from LT of 32 mo. SVR12 was achieved in 90% of patients,

with rates around 70% in patients with advanced fibrosis[119]. While non-significant changes have been reported with tacrolimus use, up to 6-fold increases in SMV concentration have been noted in association with cyclosporine, due to inhibition of cytochrome P450 3A, ion-transporting polypeptide, and p-glycoprotein. Based on this data, SMV/SOF is preferred in patients receiving tacrolimus and represents a valid option in patients with impaired renal function or anemia who may not tolerate RBV. Additional data on SIM/SOF ± RBV came from a subgroup of 143 LTR from the TARGET cohort including 57% patients with cirrhosis. SVR4 rates were 94% among non-cirrhotic patients and 86% in patients with cirrhosis, showing a high level of concordance between cure rates obtained from clinical trials *vs* from real-life observational cohorts[120].

Treatment of LTR with Human immunodeficiency virus/ HCV coinfection

After the introduction of highly active antiretroviral therapy, ESLD has become the main cause of death among human immunodeficiency virus (HIV)/HCV-coinfected patients[121]. In patients that are not successfully treated for HCV, HIV infection accelerates the course of liver disease and increases the mortality rate[122]. LT is an effective treatment for HIV/HCV-coinfected patients with severe liver disease; LTR, however, display significantly lower survival rates (around 55% at 5 years) compared with HCV-monoinfected patients[123]. HIV infection alone has a minor impact on the outcome of organ transplantation; in fact, excellent results are reported among HIV monoinfected (or HIV/HBV-coinfected) patients undergoing LT, and better outcomes for HIV-positive compared to HCV-infected recipients of organ transplant have been recently demonstrated[124]. HIV/HCV coinfection, however, accelerates post-LT progression towards fibrosis and liver decompensation[125]. Furthermore, interactions between immunosuppressants and antiretrovirals *via* modulation of cytochrome P450 contribute to higher rates of acute graft rejections compared to non-HIV infected patients. Although new classes of antiretrovirals with limited interactions, such as integrase inhibitors and CCR5 receptor antagonist, are currently used in HIV/HCV-coinfected LTR, the presence of multiple and reciprocal drug-drug interactions or pathological conditions can still affect plasma drug concentrations[126,127]. Moreover, HIV/HCV-coinfected patients have historically shown high adverse effects and discontinuation rates following anti-HCV treatment[128,129]. Overall, poor survival along with limited effective therapeutic options still represent major barriers to LT in this cohort[130,131]. Data reporting the results of anti-HCV treatment in HIV/HCV-coinfected LTR is scarce. Responses to Peg-IFN/RBV were significantly lower in HCV/HIV-coinfected LTR compared to monoinfected transplant recipents (10% *vs* 33%, respectively), particularly among genotype 1 patients[129]. Nevertheless, HIV/HCV-coinfected patients achieving SVR showed survival rates up to 79%. The use of BOC and TVR in 7 HIV/HCV-coinfected LTR with severe HCV recurrence demonstrated 60% SVR and no response, respectively, along with high rates of SAE[132]. Preliminary results on SOF/RBV compassionate use, instead, showed SVR4 of 100% and good tolerability in 7 HIV/HCV-coinfected LTR[133].

Thanks to an improved efficacy, safety, and tolerability in HIV and transplant patients, the newly approved antiviral therapies have the potential to transform the treatment outcomes of HIV/HCV-coinfected patients with liver complications. Data from nontransplant patients suggests that HIV infection itself does not negatively impact SVR. Two trials involved a heterogeneous population of HIV/HCV-coinfected patients treated with SOF/RBV including different genotypes, patients with compensated cirrhosis, and treatment experienced patients. SVR12 were 90% in genotype 2 (irrespective of treatment duration) and above 80% among the other genotypes[129,134]. High relapse rates in genotype 1 patients, however, suggested that dual DAA combinations is preferred in this group; overall, lowest SVR were displayed in patients with genotype 3 treated for 12 wk and in patients with genotype 1 and cirrhosis. Therapy duration of 12 wk for genotype 2 and 24 wk for genotype 3 and 4 are recommended. Low rates of SAE and discontinuation (8% and 2.5%, respectively) were reported. Other key studies in this cohort included the combination of SOF/LDV administered for 12 wk to 50 GT1 coinfected patients with optimal baseline conditions (*e.g.,* absence of cirrhosis or previous treatment failures) showing SVR rates close to 100%[135]. The same combination showed SVR rates of 94% and 97% in cirrhotic and treatment-experienced patients, respectively, in a study encompassing 335 coinfected HIV-HCV patients[136].

In a trial including 20% of patients with cirrhosis, HIV/HCV-coinfected patients receiving paritaprevir/r/ombitasvir, dasabuvir and RBV had SVR rates above 90%, irrespective of treatment duration[137]. Combination of grazoprevir and elbasvir showed comparable results between monoinfected and coinfected subjects (SVR12 of 93% *vs* 97% with RBV and 98% *vs* 87% without RBV, respectively)[138]. Data on SMV use in coinfected patients is limited; its use in 12 HIV/HCV-positive patients showed SVR of 92%[139].

DCV/SOF regimens in HIV/HCV-coinfected patients showed SVR of 98% when administered for 12 wk in treatment-experienced patients. Shorter regimens (*e.g.,* 8 wk), however, were associated with high relapse rates especially in cirrhotic patients[140].

Although some trials were limited by a small number of patients or presented only interim results, anti-HCV treatment appeared to have similar efficacy among coinfected and monoinfected patients. Therefore, the new guidelines do not consider HIV/HCV coinfected

patients as a special population and recommend DAA-based treatments irrespective of HIV status. Among different anti-HCV regimens, paritaprevir/ritonavir/ombitasvir plus dasabuvir was the most susceptible to drug interactions with antiretrovirals. SMV can also cause drug interactions with PI, efavirenz, etravirine, and ciclosporin; conversely, minor or non-clinically significant interactions were seen with DCV, SOF, or LDV[141]. LDV/SOF, however, may increase tenofovir levels when associated with ritonavir-boosted HIV PI and its use is not recommended in patients with estimated CrCl < 60 mL/min.

Recently, recommendations for the treatment of HIV/HCV-coinfected LTR with recurrent HCV disease have been published by a group of experts[142]. Based on the efficacy and the low potential for drug interactions, SOF/RBV and SOF/daclatasvir ± RBV were identified as potentially preferred regimens in HIV/HCV-coinfected LTR[142].

Updated databases and publications detailing the interactions between anti-HCV regimens and antiretrovirals are available and should always be consulted for the management of coinfected patients[112,116].

CONCLUSION

Until recently, a well-tolerated and effective treatment protocol for the recurrence of HCV infection following LT has been an important unmet clinical need. The excellent response rates from new DAA combination therapies have opened new scenarios for patients with HCV-related advanced liver disease. Difficult-to-treat patients (including LT candidates and recipients), however, have been understudied in recent trials. Even if data is limited in these patient populations, overall cure rates in clinical practice compared to clinical trials remained high, suggesting that even in real-life patients the high SVR rates can be reproducible. The benefits provided by the new anti-HCV regimens apply to both pre-transplant and post-transplant periods. Good safety profiles, high SVR rates, and MELD score improvement among patients with CTP C cirrhosis on waiting list shown by SOF-based regimens may lead to a delay in organ allocation. This result was not reported with Peg-IFN/RBV and could be attributed to IFN-free regimes that lack the catabolic effects induced by IFN, hence allowing a significant clinical improvement over a short time frame. Among LTR, early antiviral treatment after transplant (*e.g.,* from 6 to 12 mo) may become standard and reduce the occurrence of advanced CPT scores that have been correlated to a limited response to anti-HCV treatment. IFN-free, DAA combinations may represent the future ideal option for patients on transplant waiting list and post-LT. Given that a high proportion of patients in recent trials still required concomitant erythropoietin or blood transfusions, the possibility to eliminate RVB appears very attractive. Nevertheless, drawbacks and open questions still apply to the scenario of new anti-HCV drugs. While compounds such as SOF, GS-5816, and daclatasvir have activity against various genotypes, most combinations are mainly active against genotype 1. Among patients with genotype 3 and cirrhosis, however, reduced SVR were reported. Furthermore, a growing number of patients who have failed under DAA-based therapy will need more potent treatment options in the near future. Specifically, cirrhotic genotype 1 patients with a history of previous HCV treatment failure represent a challenging population. Among patients with cirrhosis, including LTR, unanswered questions concern the need for RBV association to new therapies and the requirement to pursue longer treatment duration (12 wk *vs* 24 wk). Renal impairment, that often complicates ESLD, has not been fully addressed in the recent studies and necessitates further attention. Overall, a proportion of patients with advanced liver disease will progress towards ESLD despite the achievement of SVR, and the impact of new therapies is likely to be limited among patients with HCC. Finally, availability restrictions along with new treatments high cost still have a big impact on patient populations who necessitate prioritized treatment.

In conclusion, the availability of new options in the treatment of HCV infection is likely to have a major impact in liver transplant candidates and recipients. Further studies employing new DAA combinations in the treatment of patients with decompensated cirrhosis, HIV/HCV coinfection, and chronic kidney disease are awaited in order to improve the management of difficult-to-treat populations that often require urgent treatment.

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