

Treatment of chronic hepatitis C in liver transplant candidates and recipients: Where do we stand?

Chrysoula Pipili, Evangelos Cholongitas

Chrysoula Pipili, Division of Nephrology, Royal Infirmary of Edinburgh, Scotland EH16 4SA, United Kingdom
Evangelos Cholongitas, 4th Department of Internal Medicine, Medical, Medical School of Aristotle University, Hippokraton General Hospital of Thessaloniki, 54642 Thessaloniki, Greece

Author contributions: Pipili C and Cholongitas E contributed equally in writing and editing of the article.

Conflict-of-interest: None.

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Correspondence to: Evangelos Cholongitas, Assistant Professor of Internal Medicine, 4th Department of Internal Medicine, Medical School of Aristotle University, Hippokraton General Hospital of Thessaloniki, 49, Konstantinopoleos Street, 54642 Thessaloniki, Greece. cholongitas@yahoo.gr
Telephone: +30-23-10892110
Fax: +30-23-10992940

Received: December 13, 2014
Peer-review started: December 13, 2014
First decision: January 8, 2015
Revised: May 18, 2015
Accepted: June 1, 2015
Article in press: June 2, 2015
Published online: June 28, 2015

Abstract

The first generation direct antiviral agents (DAAs) highlighted substantial prognosis improvement among liver transplant (LT) candidates and recipients with recurrent hepatitis C virus (HCV) infection. During

2014, second generation DAAs are associated with high sustained virological response rates (> 95%), shortened duration courses and relatively few toxicities. In keeping with the currently available data, patients with decompensated cirrhosis awaiting LT is preferable to be treated with interferon-free, new generation DAAs, with or without ribavirin combinations. Although data about the safety of new DAAs combinations in this patient population are limited, sofosbuvir and daclatasvir pharmacokinetics do not appear to change significantly in moderate or severe liver impairment, while other new DAAs (simeprevir, asunaprevir) seem to be contraindicated in patients with severe liver impairment (Child-Pugh class C). On the other hand, sofosbuvir should not be given in patients with glomerular filtration rate \leq 30 mL/min, but ongoing trials will clarify better this issue. With the objective that newer antiviral combinations will yield safer and more efficient manipulation of HCV recurrence post-transplant, the European Association for the Study of the Liver has recently updated its recommendations towards this direction. Nevertheless the new antivirals' high cost may be the biggest challenge to their implementation worldwide.

Key words: Liver transplantation; Decompensated cirrhosis; Hepatitis C; New antiviral agents; Sofosbuvir; Simeprevir; Daclatasvir; Recurrent hepatitis C

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Core tip: Treatment landscape for liver transplant (LT) candidates and recipients with chronic hepatitis C is rapidly shifting due to novel updated data on direct antiviral agents (DAAs); Patients with decompensated cirrhosis awaiting LT should be treated with the interferon (IFN)-free, new generation DAAs, with or without ribavirin (RBV) regimens; IFN-free combinations of sofosbuvir with other novel DAAs with or without RBV led to remarkable on-treatment virological response

along with minimal adverse effects “on difficult to treat” LT recipients with recurrent hepatitis C - those with chronic hepatitis C genotype 1, decompensated cirrhosis with Child-Pugh stage B and C as well as previously intolerant or non responsive to IFN therapy; Evidence regarding the efficacy and safety of novel combinative treatments although are very promising, refer still to patients case series.

Pipili C, Cholongitas E. Treatment of chronic hepatitis C in liver transplant candidates and recipients: Where do we stand? *World J Hepatol* 2015; 7(12): 1606-1616 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v7/i12/1606.htm> DOI: <http://dx.doi.org/10.4254/wjh.v7.i12.1606>

INTRODUCTION

Hepatitis C virus (HCV) infection is the leading liver cause of death worldwide and the main indication for liver transplantation (LT)^[1-3]. It also diminishes overall and graft survival in LT recipients resulting in shorter survival comparing with other LT recipients^[4,5]. Ideally, viral load elimination prior to LT hampers graft loss from chronic hepatitis C (CHC) recurrence^[6]. In the absence of an HCV vaccine to prevent infection and with therapy until very recently limited to interferon (IFN)-based regimens, most HCV-infected candidates for LT patients remained untreated.

Direct antiviral agents (DAAs) represent a striking innovation in HCV treatment. The first generation DAAs, boceprevir and telaprevir, act mainly as NS3-4A serine protease inhibitors and have been in use since 2011. When combined with pegylated IFN (Peg-IFN) and ribavirin (RBV) lead to 30% increase of sustained virological response (SVR) on CHC patients with genotype 1 treated for the first time and to 50%-60% increase on those who experienced at least one episode of relapse compared to the standard of care (Peg-IFN plus RBV)^[7]. However, first generation DAAs present significant draw backs such as limited efficacy on HCV genotype 1, absolute co-administration with Peg-IFN and RBV, frequent drug-to drug interactions and toxicity, particularly in patients with underlying cirrhosis^[7]. Patients with decompensated cirrhosis who are on the transplant list should be considered for IFN-free, ideally RBV-free therapy because both Peg-IFN and RBV are associated with poor tolerability and many side effects mainly due to the splenomegaly-related pancytopenia^[6].

Other classes of DAAs targeting different steps of HCV replication have been approved more recently, including nucleotide polymerase (NUC-NS5B) inhibitors, non-nucleotide polymerase (non-NUC-NS5B) inhibitors and NS5A inhibitors. Several dual and triple DAA regimens are in clinical development in patients before and after LT suggesting that these regimens will dramatically reduce the impact of recurrent HCV post LT^[8].

Within 2014, three new DAAs were licensed for

use in combined therapies against HCV infection in the European Union. These include sofosbuvir, (Sovaldi, Gilead Sciences) which represents the first NS5B HCV polymerase inhibitor that has pangenotypic antiviral activity and a high genetic barrier to resistance^[9]; simeprevir (Olysio, Janssen), a second-wave NS3/4A protease inhibitor; and daclatasvir (Daklinza, BMS), an NS5A inhibitor^[6]. In addition, other DAAs are currently under consideration and their final approval is waiting in the first half of 2015 (Table 1). All these DAAs have been evaluated with or without Peg-IFN ± RBV. Although scarce data is available in LT candidates and recipients, novel DAAs combinations seem more efficacious and better-tolerated option. Nevertheless, cost limitations across various health insurances may avert their use. The current review updates treatment for patients with CHC before and after LT.

HCV positive LT candidates

The aim of antiviral therapy before LT is the undetectable HCV RNA at the time of LT or SVR before LT^[10]. Peg-IFN and RBV was the standard of care for patients with CHC up to 2011. Indeed they reduced cirrhosis driven complications such as HCC and improved the abnormal histological changes^[10,11], but in an inadequate percentage of patients^[12-16]. Generally, SVR rates are lower in patients with cirrhosis ranging 40%-50% for Child-Pugh (CP) class A and 7%-26% for CP class C^[17-20] and in patients with genotypes 1 and 4 compared with genotype 2 and 3 patients (51% vs 61%)^[20] while a reduction on SVR is evident regarding the level of fibrosis (Tables 2 and 3).

Peg-IFN-based treatment has also been associated with poor tolerability and lots of adverse effects^[3,5]. These include neuropsychiatric disorders and mainly pancytopenia^[20], requiring erythropoietin and granulocyte colony-stimulating factors^[21,22]. Of note, LT candidates with HCV compensated cirrhosis are more prone to Peg-IFN- and RBV-related hematologic toxicities, because splenomegaly caused by portal hypertension enhances the risk for cytopenias^[23]. Therefore, Peg-IFN and RBV dose adjustment and close monitoring is recommendable. More specifically, patients with CP score B require treatment tailoring decisions focused on type of genotype, level of viral load and first or repeat antiviral treatment^[10].

A triple therapy with the addition of first generation DAAs is the preferred choice for patients with genotype 1 when newer DAAs are not available^[6]. Boceprevir and telaprevir are better therapeutic choice for patients with genotype 1 ensuring excellent efficacy and prognosis compared to Peg-IFN and RBV treatment. Data showed that triple therapy increased SVR rates in naïve and previously treated patients with genotype 1 between 68%-75% and 59%-88% respectively^[24-28]. Boceprevir therapy also offers the possibility of shortened duration therapy for rapid responders, defined by an undetectable plasma HCV RNA level at treatment week 8^[24]. One should notice that DAAs should not be applied as monotherapy and their dose should not be reduced,

Table 1 Direct acting antivirals commenced on patients with decompensated cirrhosis or recipients after liver transplantation

Approved protease inhibitors	
Boceprevir	NS3-4A serine protease inhibitors
Telaprevir	Second-wave NS3/4A protease inhibitor
Simeprevir	
Approved NS5A inhibitors	
Daclatasvir	NS5A inhibitor
Approved NS5B RNA-dependent RNA polymerase nucleotide inhibitor	
Sofosbuvir	NS5B RNA-dependent RNA polymerase nucleotide inhibitor
Newer DAAs evaluated in combination regimens without Peg-IFN	
Ledipasvir (formerly GS-5885)	NS5A inhibitor
ABT-450	NS3/4A protease inhibitor
Ombitasvir (formerly ABT-267)	NS5A inhibitor
Dasabuvir (formerly ABT-333)	Non-nucleoside NS5B polymerase inhibitor

Peg-IFN: Pegylated interferon.

stopped and then restarted^[29]. However, high rates of serious adverse events, discontinuation and deaths have been recorded^[30]. The adverse effects included anaemia, metallic taste, infection and rash which were more evident in patients with cirrhosis^[24-28]. For this reason the administration of the triple therapy remains of high risk in patients with cirrhosis. Anaemia is considered positive predictor of SVR in patients receiving the triple regimen and should be corrected with erythropoietin and reduction of RBV dose^[31-33] without any change in boceprevir or telaprevir administration.

The data regarding the efficacy and safety of triple therapy to HCV patient with decompensated cirrhosis are very limited. Verna *et al*^[34] treated 29 patients with cirrhosis CP class A (62%) or B (38%) while waiting on the transplant list with telaprevir (93%) or boceprevir-based (7%) triple therapy for a median (range) of 27 (3-50) wk, including a Peg-IFN and RBV lead-in phase in 18%. Overall SVR at 12 wk was 52%, including patients who completed a full course of therapy, but 28% of patients require hospital admission because of treatment complications including decompensation of liver disease, variceal hemorrhage, cholecystitis, optic neuritis and anemia requiring transfusion^[34]. The efficacy and the safety of triple therapy have been tested in patients with mildly decompensated cirrhosis as well^[35]. SVR at 12 wk was achieved by 35% of patients with CP ≥ 6 vs 54% of those with CP = 5^[35]. Furthermore, 25% of patients with compensated cirrhosis discontinued treatment early due to adverse events, while high proportion required drug dose reductions and hospitalizations due to side effects^[35]. Although a French multicenter phase II trial is being assessing the safety and the efficacy of boceprevir-based triple therapy in patients with genotype 1 and a baseline MELD score 18 on the waiting

Table 2 Doses of antivirals in liver transplant candidates and recipients

Peg-IFN- α 2a	180 μ g/wk, subcutaneous	Renal adjustment
Peg-IFN- α 2b	Weight-based 1.5 μ g/kg per week, subcutaneous	No CNI adjustment
Ribavirin	Weight-based, 1000 mg in patients < 75 kg, 1200 mg in patients \geq 75 kg, orally twice a day	
Boceprevir	800 mg orally three times a day	No renal adjustment
Telaprevir	1125 mg orally twice a day	CNI adjustment
Sofosbuvir	400 mg daily, orally	
Daclatasvir	60 mg daily, orally	No renal adjustment ¹
Simeprevir	150 mg daily, orally	No CNI adjustment ²

¹Sofosbuvir only in patients with glomerular filtration rate > 30 mL/min;

²Simeprevir should not be given with cyclosporine. CNI: Calcineurin inhibitor; Peg-IFN: Pegylated interferon.

list^[36], it is apparent that IFN-free therapies are highly desirable for patients with decompensated disease^[34,35].

In fact, the treatment chances of critical CHC candidates for LT will be very high should second generation DAAs is applicable. Sofosbuvir, a nucleotide HCV polymerase inhibitor, is now available and offers better tolerability and efficacy across all HCV genotypes making sustained clearance of HCV deliverable to a much larger number of infected individuals^[8]. We are at the beginning of an era where combinations of DAAs may pave the way for IFN-free regimens, even improving the viral clearance rate to near 100%. Evidence comes from the following four trials^[37-40]. In the open label phase II study of Curry *et al*^[37] 61 CHC candidates with HCC and normal liver function tests (CP score \leq 7) commenced on sofosbuvir (400 mg/d) and RBV (based on their weight) until LT for a maximum of 48 wk. Thirty six out of the 40 patients who underwent LT achieved viral load below 25 IU/mL pre LT. In the view of excellent tolerability, 96% had undetectable HCV RNA and no viral recurrence at four weeks post LT. Nevertheless, 69% achieved SVR and 27% had HCV recurrence, 12 wk post LT. Curiously, one patient undergone second LT died and one presented anemia related to RBV.

Given the high mortality due to HCV recurrence after LT, the evidence that sofosbuvir and RBV before LT prevented the recurrence of CHC after LT in 70% of patients who had undetectable HCV RNA prior to LT, provide great hope for patients in need. In the randomized open label study of Afdhal *et al*^[38] 50 CHC with genotypes 1-4 either commenced on sofosbuvir plus RBV for 12 mo or were observed for 6 mo and then treated. Patients' characteristics included portal hypertension plus/or minus decompensated liver disease, CP score 5-10 and MELD score > 13. Undetectable HCV-RNA was achieved in 100% for CP class A and 93% for CP class B after 6 mo of treatment. No patient experienced treatment breakthroughs. Ultimately, in the study of Gane *et al*^[39] 20 patients with CHC genotype 1 and CP class B received sofosbuvir \pm RBV combined with the newer NS5A inhibitor ledipasvir for four weeks

Table 3 Treatment of liver transplant candidates with hepatitis C^[6]

Cirrhosis CP A, all HCV genotypes Sofosbuvir + RBV until LT	Peg-IFN + RBV + sofosbuvir for 12 wk	RBV + sofosbuvir + daclatasvir for 12 wk
Cirrhosis CP B and C, all HCV genotypes Sofosbuvir + RBV until LT	IFN contraindicated	RBV + sofosbuvir + daclatasvir for 12 wk

CP: Child-Pugh; HCV: Hepatitis C virus; LT: Liver transplant; RBV: Ribavirin; Peg-IFN: Pegylated interferon.

Table 4 Major studies of interferon-free regimens for treatment of hepatitis C virus positive liver transplant candidates reported in 2014

Ref.	n	CP score	Antiviral scheme	Virological response
Curry <i>et al</i> ^[37]	61	≤ 7	SOF + RBV for 48 wk or until LT	69% (12 wk after LT)
Gane <i>et al</i> ^[39]	20	7-9	SOF ± RBV + ledipasvir for 12 wk	89% (SVR 4 wk)
Flamm <i>et al</i> ^[40]	108	Decompensated cirrhosis (range: 7-12)	SOF + RBV + ledipasvir for 12 or 24 wk	87% and 89%, respectively (SVR 12 wk)
Afdhal <i>et al</i> ^[38]	50	5-10	SOF + RBV for 48 wk	100% CP class A 93% CP class B at 24 wk under treatment

n: Number of patients; CP: Child-Pugh; SOF: Sofosbuvir; RBV: Ribavirin; SVR: Sustained virological response.

(preliminary data for the ongoing Electron Study). High percentage (89%) achieved SVR so far (at four weeks) with good safety and tolerance profile (there were no treatment discontinuations). Similarly, sofosbuvir, ledipasvir and RBV for 3 or 6 mo were well tolerated and resulted in high SVR (87% and 89%, respectively) in 108 patients with decompensated cirrhosis CP class B or C^[40]. Interestingly, Donato *et al*^[41] reported undetectable HCV RNA for 24 wk after treatment discontinuation in a LT recipient treated prior LT - on the waiting list- over LT and post LT for a total period of 24 wk with the combination of sofosbuvir and RBV (Table 4).

Based on the currently available data, patients with decompensated cirrhosis awaiting LT should be treated with the IFN-free, new generation DAAs, with or without RBV regimens. Although more data are needed about the safety of new DAAs drug combinations in this patient population, it seems that the pharmacokinetics of sofosbuvir and daclatasvir do not appear to change significantly in moderate or severe liver impairment^[42], while other new DAAs (simeprevir, asunaprevir) seem to be contraindicated in patients with severe liver impairment (CP class C). On the other hand, sofosbuvir should not be given in patients with GFR ≤ 30 mL/min, but ongoing trials will clarify better this issue. With the objective that newer drug combinations will yield safer and more efficient prevention of HCV recurrence post-transplant and the - so far poorly treated - patients with low MELD scores and HCC will benefit most^[6], treatment recommendations for LT candidates are updated as below: Patients with conserved liver function (CP class A) in whom the indication is HCC for LT is strongly recommended to be treated with daily weight-based RBV (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively) and daily sofosbuvir until LT. Otherwise, they should be offered a 12-wk treatment prior to LT with the combination of Peg-IFN, RBV and sofosbuvir or the combination of daily weight-based

RBV, daily sofosbuvir and daily daclatasvir^[6]. Candidates with more advanced decompensated cirrhosis (CP class B and C), should be commenced only in IFN-free regimens; *i.e.*, daily weight-based RBV and daily sofosbuvir for minimization post-LT HCV recurrence; for genotypes 1 to 4 the triple combination of daily weight-based RBV, daily sofosbuvir and daily daclatasvir until LT in experienced centres under close monitoring^[6]. Both sofosbuvir and daclatasvir do not need dose adjustments in patients with CP class B or C disease. Their most frequently reported side effects were fatigue, headache, nausea and anemia, the latter attributable to the co-administration of RBV^[6,43].

HCV positive LT recipients

Reinfection of liver allograft is universal resulting in acceleration of HCV recurrence compared with non-LT patients leading in 70% decompensation vs 10% in other immunocompetent groups three years post-transplant^[44]; graft loss and lower survival rates^[45,46]. HCV recurrence is the most frequent cause of death and accounts for the two thirds of graft failures in patients transplanted for HCV infection^[39]. Fibrosing cholestatic hepatitis is the most severe aggressive form of HCV recurrence affecting 5%-8% of LT recipients^[47]. It is characterized by high viral load levels and extensive dense portal fibrosis extending into the sinusoidal spaces, ductular proliferation, cholestasis and mononuclear inflammation^[48]. Its prognosis is very poor if recipients do not respond to antiviral treatment (Tables 2 and 5).

Several strategies, including the new generation of antivirals, the optimal donor and the immunosuppressant selection, have been applied to improve outcomes post LT. Negative predictive factors associated with aggressive recurrent HCV infection and graft loss are the high HCV RNA levels in both serum and liver at the time of or early post-LT, female gender and older donor age, steatosis of the graft as well as the degree

Table 5 Treatment of hepatitis C virus recurrence post liver transplant

IFN-free: Sofosbuvir + RBV (HCV genotype 2 for 12-24 wk); sofosbuvir + daclatasvir ± RBV (HCV genotypes 1, 3-6 for 12-24 wk); sofosbuvir + simeprevir ± RBV (HCV genotypes 1, 4 for 12-24 wk)		
In case of restriction applying first generation DAAs		
Fibrosis metavir stage 3-4	Genotype 2/3	Genotype 1
Genotype 1a		Fibrosis metavir stage 2
IL-28B polymorphism		Predictors of poor response
Fibrosing cholestatic hepatitis	Peg-IFN plus RBV	Peg-IFN plus RBV plus boceprevir or telaprevir
Non responders to previous treatments	Monitor closely Hb, WBC, PLTs, CNI levels, renal function	
	Consider	
	Administration of blood transfusions, EPO, CSGF	
	Decrease of RBV dose	
	Renal dose adjustment	
	Decrease of CNI dose	

IFN: Interferon; RBV: Ribavirin; CNI: Calcineurin inhibitor; HCV: Hepatitis C virus; Peg-IFN: Pegylated interferon; DAA: Direct antiviral agent; WBC: White cells blood count; PLTs: Platelets; EPO: Erythropoietin; CSGF: Granulocyte-colony stimulating factor.

of human leukocyte antigen matching of the donor and recipient^[49,50]. Moreover, immunosuppressant selection is considered a major factor contributing to acceleration of HCV recurrence. While methyl prednisolone pulses for treatment of acute rejection could drive aggressive HCV recurrence ending up to graft loss, sirolimus could result on HCV RNA elimination without additional antiviral treatment^[51,52]. Ultimately, everolimus may offer a benefit for posttransplant HCV-related fibrosis progression^[53]. Cyclosporine is considered to have advantage over the other immunosuppressants, because of potential antiviral action (the target protein of cyclosporine, cyclophilin A is involved in the HCV replication)^[54]; the enhancement of SVR in LT recipients treated with the dual therapy^[55] and the fewer interactions with the triple regimen. Steroid free regimens have been also tried; although they were safe and effective, they did not influence HCV recurrence^[56,57]. Nevertheless, many of these issues might have limited impact in the era of the newer DAAs, since the majority of patients with HCV recurrence can effectively be treated.

Preemptive prophylaxis for CHC recurrence post LT is not recommendable so far with Peg-IFN-based regimens, because as determined by randomized trials the therapeutic cost is high, tolerability is poor and no additional therapeutic effect is gained^[58-60]. Nevertheless, new DAAs clinical application this may change this therapeutic strategy in the near future. The presence of significant fibrosis or portal hypertension one year after transplantation is predictive of rapid disease progression and graft loss, requiring urgent antiviral treatment^[61,62]. Fibrosing cholestatic hepatitis and significant fibrosis^[63] determined by METAVIR score > F1^[64], liver stiffness > 8.7 kPa^[65] and hepatic venous gradient > 6^[60] are additional indications for antiviral treatment. Of note is the fact that patients with fibrosis level > 3 cannot tolerate Peg-IFN-based therapy^[66]. Timely diagnosis of HCV recurrence based on histology is also recommendable, but should be properly differentiated with acute liver rejection since pathology is similar but treatment distinct^[67]. Simultaneous use of regular protocol biopsies, transient elastography and fibrosis

markers are necessary to determine the progression of rejection and/or fibrosis^[22].

The therapeutic strategy for treatment of HCV recurrence post LT continues to be updated. Initially, Peg-IFN combined with RBV was the only therapeutic choice. SVR stabilization has been achieved in only 30% of recipients^[62-71] and IFN on the top of intense immunosuppression lead to multiple episodes of sepsis, acute and chronic rejection and plasma cell hepatitis^[10,63,68]. Secondly, the addition of first generation DAAs on the classical Peg-IFN and RBV regimen was applied to LT recipients with genotype 1, non-responders to dual therapy, cases of METAVIR fibrosis stage 2, and cholestatic hepatitis^[63,72]. The results were satisfactory and encouraging^[63]. Seven studies^[73-79] (including four multicenter) suggested that triple therapy was effective in LT recipients, particularly those experiencing severe recurrence, demonstrating SVR in 50%-91% when administered for 12 to 66 wk (Table 6). One major benefit of the triple therapy was the success in treating recipients with fibrosing cholestatic hepatitis^[73]. Nevertheless, serious adverse and few fatal events were recorded. The most common side effect was anaemia (40%-50%) required red blood cell transfusions, erythropoietin and/or RBV dose reduction. The mechanism of anaemia was the combination of hemolysis with suppression of bone marrow. In cirrhotic non-responding patients severe infections have been marked in the context of neutropenia (pneumocystosis, aspergilosis, urinary tract infections and erysipelas have been noted). On this ground, severe liver disease may be a contraindication for triple regimen or may require antibiotic prophylaxis and colony-stimulating factors^[73]. Kidney insufficiency has also been reported in 13%-38%^[73,74].

Furthermore drug-drug interactions remain a crucial clinical issue. Close monitoring of daily calcineurin inhibitors (CNIs) levels and reduction of CNIs dose was required^[80]. CNI trough level is increased when first generation DAAs are initiated because they may inhibit cytochrome P450 3A4 and P-glycoprotein. With boceprevir the average reductions were about 2-fold and 5-fold with cyclosporine and tacrolimus respectively, while

Table 6 Major studies tested the efficacy of first generation direct antiviral agents combined with peg-interferon and ribavirin in liver transplant recipients

Ref.	Year of publication	No. of patients	Sustained virological response
Coilly <i>et al</i> ^[73]	2013	37	50% (20% for telaprevir and 71% for boceprevir)
Pungpapong <i>et al</i> ^[74]	2013	60	56% (67% for telaprevir and 45% for boceprevir)
Werner <i>et al</i> ^[75]	2012	9	89%
Stravitz <i>et al</i> ^[76]	2013	122	28%
Ann Brown <i>et al</i> ^[77]	2013	46	60%
Faisal <i>et al</i> ^[78]	2014	76	59.5%
Werner <i>et al</i> ^[79]	2014	14	50%

with telaprevir the interactions were more potent around 3-fold and 23-fold with cyclosporine and tacrolimus respectively^[73]. Great attention is needed at the time of DAAs discontinuation, increasing the CNI dose the next day and measuring CNI levels at least every 48 h until steady state to be achieved. mammalian target of rapamycin inhibitors are also metabolized by CYP3A4; the clearance of everolimus was reported to decrease by 55% when boceprevir is commenced^[80]. No information on the interactions between mycophenolate mofetil and DAAs is available. In healthy individuals prednisone area under the curve was increased by 22%^[81].

So far, triple antiviral therapy with first generation DAAs was less effective in patients with genotype 1a, TT/CT interleukin-28B polymorphism and non responders to previous peg-IFN/RBV regimen^[82]. However, the approval of sofosbuvir headed forward the care of naive and treatment experienced LT recipients with CHC recurrence with excellent tolerability, without interaction with the immunosuppressive regimen and potent antiviral activity across a broad range of HCV genotypes^[43,83]. Particularly, in the single-arm open-label pilot study of Samuel *et al*^[83], 40 LT recipients with CHC recurrence after 6 mo of LT treated with sofosbuvir plus RBV for maximum of 6 mo. Thirty-three (83%) patients had genotype 1, 16 (40%) were cirrhotic and 9 (23%) patients were previously on telaprevir or boceprevir combined regimens. All patients (100%) had undetectable HCV RNA after a month of treatment and 70% achieved SVR. Rejection and CNIs dose adjustment were not needed. Only fatigue, anemia, arthralgia and diarrhea were of note. Forns *et al*^[43] demonstrated significant antiviral efficacy associated with disease amelioration in 87 LT recipients [72 (83%) presented HCV genotype 1] with severe CHC recurrence including fibrosing cholestatic hepatitis. Fifty-seven (65%) were treated with sofosbuvir combined only with RBV, while 30 (35%) received additional Peg-IFN for up to 48 wk. SVR at 12 wk was achieved in 47 (54%) of LT recipients treated with sofosbuvir plus RBV and in 40 (44%) of LT recipients treated with sofosbuvir plus RBV plus Peg-IFN. No drug side effects were reported. Importantly, 53 (70%) of patients had improved on treatment, 10 (13%) had stabilized and 13 (17%) died with all deaths attributed to progression of liver disease or associated complications.

More recently, very promising are the IFN-free combinations of sofosbuvir with other novel DAAs with or without RBV after LT (Table 7). Although these new DAAs may have interactions with several drugs, they have no contraindication for CNIs co-administration (only simeprevir should not be given with cyclosporine) (Tables 2 and 8). Preliminary data^[84-89] showed that they led to excellent on treatment virological response and SVR rates along with minimal adverse effects on difficult to treat LT recipients - those with CHC genotype 1, cirrhosis CP stage B and C as well as previously intolerant or non responsive to IFN therapy. More specifically, sofosbuvir plus simeprevir presented 91% SVR in LT recipients with genotype 1^[85]; Sofosbuvir and daclatasvir showed 85% on treatment virological response in LT recipients with genotype 1^[86] and major clinical improvement in 71% along with HCV RNA < 15 IU/mL in 95% at 12 wk under treatment in LT recipients with fibrosing cholestatic hepatitis^[87]; ledipasvir plus sofosbuvir plus RBV presented 96%-98% SVR in LT recipients with CHC recurrence^[88].

Ultimately, preliminary data from Coral I study^[89] showed breakthrough results in 34 LT recipients with CHC genotype 1 treated for 24 wk with the following four-drug combination: Paritaprevir (potent NS3/4A protease inhibitor identified by AbbVie and Enanta, formerly ABT-450) with ritonavir (which increases overall drug exposures of paritaprevir and enables once daily dosing) combined with Ombitasvir (potent NS5A inhibitor, formerly ABT-267) and Dasabuvir (non-nucleoside NS5B polymerase inhibitor, formerly ABT-333) and RBV. More specifically, 97.1% (33/34) achieved SVR at 4 wk and 97% (33/34) achieved SVR at 12 wk. The regimen was generally well tolerated with 1 patient discontinuing study drug due to adverse events. No deaths, no graft losses, or episodes of rejection were recorded. CNI dosing was manageable over the period of the study (Table 7).

Although data are preliminary, current EASL^[6] guidelines recommend the following therapeutic regimens to treat HCV recurrence after LT: sofosbuvir and RBV for LT recipients HCV genotype 2; sofosbuvir and daclatasvir plus/minus RBV for LT recipients HCV genotypes 1, 3-6 and sofosbuvir and simeprevir plus/minus RBV for genotypes 1, 4. All regimens should be continued for 12-24 wk and no dose adjustments are required for CNI inhibitors.

Table 7 Major studies of sofosbuvir with other novel direct antiviral agents with or without ribavirin for treatment of hepatitis C virus positive liver transplant recipients reported in 2014

Ref.	n	Patient characteristics	Antiviral scheme	Virological response	SVR	Duration (wk)
Pungpapong <i>et al</i> ^[85]	55	Fibrosis 3-4 (29%) Decompensated cirrhosis (4%) Cholestatic recurrence (15%)	SOF + simeprevir ± RBV	98% (EOT)	91%	12
Leroy <i>et al</i> ^[87] (CUIPILT)	21	Fibrosing cholestatic hepatitis	SOF + daclatasvir ± RBV (n = 13) SOF + RBV (n = 6)	95% HCV RNA < 15 IU/mL 81% were not detectable (at week 12 under treatment)	-	24
Conti <i>et al</i> ^[86]	55	Fibrosis 3-4 (33%) Fibrosing cholestatic hepatitis (7%)	SOF + daclatasvir	85% (at week 8 under treatment)	-	24
Kwo <i>et al</i> ^[89] (CORAL I)	34	Fibrosis 0-2	Paritaprevir + ritonavir + ombitasvir + dasabuvir + RBV	100% (EOT)	97%	24
Reddy <i>et al</i> ^[88]	223	Fibrosis 0-3, CP A-C	SOF + ledipasvir + RBV	-	96%-98% (CP A: 9% CP B: 83%-85% CP C: 60%-67%)	12-24

n: Number of patients included in the study; RBV: Ribavirin; SOF: Sofosbuvir; EOT: End of treatment; SVR: Sustained virological response; CP: Child-Pugh; HCV: Hepatitis C virus.

Table 8 Major drug-drug interactions of the newer direct acting antivirals for hepatitis C

DAA Sofosbuvir	Co-administration should be avoided P-glycoprotein inducers Anticonvulsants: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin; antimycobacterials: Rifampin, rifabutin, rifapentin; St. John's wort; HIV drugs: Tipranavir/ritonavir
Simeprevir	Inhibitors or inducers of CYP3A4 Antifungals: Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole; Antibiotics: Clarithromycin, erythromycin, telithromycin; Dexamethasone; Cicapride; HIV drugs: Cobicistat, efavirenz, delavirdine, etravirine, nevirapine, ritonavir and any HIV protease inhibitor
Daclatasvir	P-glycoprotein inducers Strong inducers of CYP3A4 and/or P-glycoprotein e.g., phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, rifapentine, dexamethasone, St. John's wort; HIV drugs: darunavir, lopinavir, etravirine
Sofosbuvir/ledipasvir	P-glycoprotein inducers, rosuvastatin, simeprevir

DAA: Direct acting antiviral; HIV: Human immunodeficiency virus.

CONCLUSION

Until 2011, the standard of care treatment for genotype 1 HCV was dual therapy with Peg-IFN and RBV. Unfortunately the success rate was less than 50%, and treatment was frequently associated with significant toxicity. For this reason, much effort has been invested in the development of new treatment for HCV, leading to the approval of the first generation DAAs. Triple therapy with Peg-IFN, RBV and boceprevir or telaprevir was associated with 68% SVR rates in treatment-naïve patients. Whilst the addition of these first generation DAAs marked a bright new era for the prognosis amelioration of LT candidates and recipients with recurrent HCV, there remains the potential for side effects and drug-drug interactions. During 2014, different IFN-free regimens, combinations of second generations DAAs associated with high SVR rates (> 95%), shortened duration courses and relatively few toxicities. However, the efficacy of IFN-free regimens

in patients with advanced decompensated cirrhosis waiting for LT is not yet established and their high cost may be the biggest challenge to their implementation worldwide. Immune therapies and therapeutic vaccines are very promising but still in progress. Based on the current related published data and the EASL therapeutic recommendations it was presented the rapidly shifting treatment landscape for CHC LT candidates and recipients. In the context of that treatment decisions continue to be individualized.

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P- Reviewer: Dang SS, Inoue K, Kapoor S **S- Editor:** Ji FF
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