



Interferon-free regimens for the treatment of hepatitis C virus in liver transplant candidates or recipients

Evangelos Cholongitas, Chrysoula Pipili, George Papatheodoridis

Evangelos Cholongitas, 4th Department of Internal Medicine, Medical School of Aristotle University, Hippokraton General Hospital of Thessaloniki, 54642 Thessaloniki, Greece

Chrysoula Pipili, Division of Nephrology, Royal Infirmary of Edinburgh, Scotland EH16 4SA, United Kingdom

George Papatheodoridis, Department of Gastroenterology, Athens University Medical School, Laiko General Hospital of Athens, 11527 Athens, Greece

Author contributions: Cholongitas E and Pipili C performed the literature search, wrote the first draft of the manuscript and approved the final version; Papatheodoridis GV wrote and edited the final draft of the manuscript and approved the final version.

Conflict-of-interest statement: Cholongitas E: advisor/consultant/sponsored lectures for Bristol-Myers Squibb, Gilead, Novartis; Pipili C: none; Papatheodoridis GV: grant/research support from Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Roche; advisor/consultant for Abbvie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp and Dohme, Novartis, Roche; sponsored lectures for Abbvie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp and Dohme, Novartis, Roche; Data Safety Management Board for Gilead.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

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: +30-231-0892110
Fax: +30-231-0855566

Received: March 14, 2015

Peer-review started: March 16, 2015

First decision: May 18, 2015

Revised: May 27, 2015

Accepted: July 18, 2015

Article in press: July 18, 2015

Published online: August 28, 2015

Abstract

The goal of therapy in chronic hepatitis C virus (HCV) infection is sustained virological response (SVR) which reflects HCV eradication. Treatment against HCV has dramatically improved with the recent availability of direct-acting antivirals (DAAs) including sofosbuvir, simeprevir, daclatasvir, ledipasvir/sofosbuvir, paritaprevir/ombitasvir and dasabuvir. Carefully selected combinations of these DAAs offer the potential for highly effective all-oral safe regimens even for patients with decompensated cirrhosis or liver transplant (LT) recipients. Like all current protease inhibitors, simeprevir and paritaprevir should not be used in patients with Child C cirrhosis, while sofosbuvir and ledipasvir/sofosbuvir should not be given in patients with severe renal impairment and glomerular filtration rate less than 30 mL/min. Drug-drug interactions may still occur with the current DAAs particularly in post-LT patients, in whom simeprevir should not be co-administered with cyclosporine and dose adjustments of calcineurin inhibitors are required in case of regimens including the ritonavir boosted paritaprevir. Phase II clinical trials and real life cohort studies have shown that sofosbuvir based combinations are safe and can achieve improvements of clinical status, high SVR rates and even prevention of post-LT HCV recurrence in patients with decompensated cirrhosis or LT-candidates. In the post-LT setting, sofosbuvir based regimens and the combination of paritaprevir/ombitasvir and dasabuvir have been reported to be safe and achieve high SVR rates, similar to those in non-transplant

patients, being effective even in cases with cholestatic fibrosing hepatitis. Ongoing clinical trials and rapidly emerging real life data will further clarify the safety and efficacy of the new regimens in these settings.

Key words: Hepatitis C; Direct acting antiviral agents; Liver transplantation; Decompensated cirrhosis; Sofosbuvir

© **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Treatment against hepatitis C virus has dramatically improved with the novel direct-acting antivirals (DAAs). The currently available DAAs are sofosbuvir, simeprevir, daclatasvir, ledipasvir/sofosbuvir, paritaprevir/ombitasvir and dasabuvir. IFN-free combinations of these novel DAAs with or without ribavirin give excellent sustained virological response in patients with decompensated cirrhosis awaiting liver transplantation and those with recurrence of hepatitis C post liver transplantation. More data regarding the safety and efficacy of these new DAAs are needed, but ongoing clinical trials and real life data will clarify better these issues.

Cholongitas E, Pipili C, Papatheodoridis G. Interferon-free regimens for the treatment of hepatitis C virus in liver transplant candidates or recipients. *World J Gastroenterol* 2015; 21(32): 9526-9533 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i32/9526.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i32.9526>

INTRODUCTION

Chronic hepatitis C (CHC) has infected approximately 3% of the world population^[1]. Patients with hepatitis C virus (HCV) infection can develop cirrhosis and hepatocellular carcinoma (HCC)^[2,3], while CHC is considered the leading cause for liver transplantation (LT) in many Western countries^[4]. The combination of pegylated interferon- α (pegIFN) and ribavirin (RBV) in patients with CHC had relatively low rates of sustained virological response (SVR)^[5,6], but during the last years several direct acting antiviral agents (DAAs) have increased the efficacy of antiviral therapy^[7].

The first approved DAAs (boceprevir and telaprevir) were associated with high rates of clinical complications, particularly among cirrhotic patients with serum albumin levels \leq 3.5 g/dL and platelet counts \leq 100000/mm³^[8]. Very recently, newer DAAs have been licensed by the European Medicines Agency and Food and Drug Administration to be used mainly as part of IFN-free combinations offering high SVR rates (> 95%), short treatment duration and excellent safety profiles. These agents include sofosbuvir (Sovaldi, Gilead), the first nucleotide analogue NS5B polymerase inhibitor^[9], simeprevir (Olysio, Janssen), a second-wave NS3/4A protease inhibitor (achieving SVR

in 77%-92% of genotype 1 CHC patients, compared to 46% under pegIFN plus RBV)^[10], daclatasvir (Dankliza, Bristol-Myers Squibb)^[11], a NS5A inhibitor, the co-formulation of the NS5A inhibitor ledipasvir with sofosbuvir (Harvoni, Gilead)^[12], the co-formulation of a ritonavir boosted NS3/4A protease inhibitor, paritaprevir, with the NS5A inhibitor ombitasvir (Viekirax, Abbvie) and dasabuvir (Exviera, Abbvie), a non-nucleos(t)ide NS5B polymerase inhibitor^[13] (Table 1). They are all given as one tablet daily, except for paritaprevir/ombitasvir (two tablets once daily) and dasabuvir (1 tablet twice daily). The purpose of this review is to summarize the recent findings concerning the use of the new IFN-free regimens in LT candidates or recipients with CHC.

TREATMENT OF HCV LT CANDIDATES

Post-transplant HCV recurrence is universal^[14] and undetectable HCV RNA at the time of LT is crucial for prevention of HCV recurrence and graft loss^[15]. At the same time, effective antiviral therapy could improve liver function resulting in some patients withdrawal from the transplant list, similarly to what has been observed in chronic hepatitis B patients on the list for LT. The severity of liver disease is evaluated with the MELD score or the Child-Pugh score classifying patients in class A (score 5-6), B (score 7-9) or C (score 10-15) in relation to best (A), moderate (B), or worse (C) prognosis. However, there are currently rather few data to support such an approach, especially among HCV patients with advanced decompensated cirrhosis (Table 2).

The availability of sofosbuvir started a bright era for treatment of HCV patients on the waiting list for LT. Data from studies in patients with decompensated cirrhosis exist only for sofosbuvir and ledipasvir/sofosbuvir, while real life data from the use of the combinations of sofosbuvir with simeprevir or with daclatasvir were reported recently. Although more studies with DAAs are highly needed in patients with chronic liver impairment and LT candidates, the currently results are very promising and have led in wide use of these agents in this setting.

In the first open label phase II study^[16], 61 LT candidates due to HCC with well compensated HCV cirrhosis (genotype 1-4, Child-Pugh score \leq 7, MELD score < 15) commenced on sofosbuvir plus RBV (1000 or 1200 mg/d). Among the 46 patients who received liver graft, 43 (93%) achieved HCV-RNA < 25 IU/mL at the time of liver transplantation. Of these 43 patients, 30 (70%) achieved SVR at 12 wk post-LT, 10 (23%) had HCV recurrence and 3 (7%) died. Only one of the patients with continuously undetectable HCV-RNA for at least one month before LT had recurrence of HCV infection post-LT. Additionally, the tolerance profile was excellent, since only one patient developed severe anemia attributable to RBV administration.

A more recent randomized study^[17] evaluated 25

Table 1 Main characteristics of the approved direct acting antivirals that are currently used in interferon-free regimens for the treatment of hepatitis C

DAA (commercial name), dose	Category	Dose adjustment in liver or renal impairment	Antiviral activity	CNIs co-administration	Co-administration should be avoided
Sofosbuvir (Sovaldi [®]), tablet 400 mg, once daily	NUC NS5B polymerase inhibitor	No change in hepatic impairment Contraindicated in patients with GFR < 30 mL/min	Genotypes 1-6, High genetic barrier	No change	P-glycoprotein inducers (Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin; Antimycobacterials: rifampin, rifabutin, rifapentin; St. John's wort; HIV drugs: Tipranavir/ritonavir) 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) P-glycoprotein inducers
Simeprevir (Olysio [®]), tablet 150 mg, once daily with food	NS3/4A protease inhibitor	Contraindicated in Child class C No change in renal impairment	Genotypes 1, 4, Low genetic barrier	Contraindicated with cyclosporine	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)
Daclatasvir (Daklinza [®]), tablet 60 mg, once daily	NS5A inhibitor	No change in liver or renal impairment	Genotypes 1,3,4, Low genetic barrier	No change	P-glycoprotein inducers, rosuvastatin, simeprevir
Ledipasvir/Sofosbuvir/ (Harvoni [®]), tablet 90/400 mg, once daily	NUC NS5B polymerase inhibitor + NS5A Inhibitor	No change in hepatic impairment Contraindicated in patients with GFR < 30 mL/min	Genotypes 1,3,4, High genetic barrier	No change	P-glycoprotein inducers, gemfibrozil, lovastatin, simvastatin, oral midazolam, triazolam, pimozone, ethinyl estradiol-containing oral contraceptives, sildenafil for pulmonary hypertension
Paritaprevir/Ritonavir/ Ombitasvir (Viekirax [®]), tablet 75/50/12.5 mg, x 2 once daily with food	Ritonavir boosted NS3/4A protease inhibitor/NS5A inhibitor	No safety and efficacy data in Child class B, Contraindicated in Child class C No change in renal dysfunction	Genotypes 1, 4, Genetic barrier depending on HCV genotype	Cyclosporine: 20% of pretreatment total daily dose; tacrolimus: 0.2 mg/72 h or 0.5 mg once weekly	
Dasabuvir (Exviera [®]), tablet 250 mg, every 12 h	Non-NUC NS5B polymerase inhibitor		Genotype 1, Low genetic barrier		

NUC: Nucleos(t)ide analogue; CNI: Calcineurin inhibitor.

genotype 1-4 CHC patients who received sofosbuvir plus RBV for 48 wk and 25 patients who were observed for 24 wk. All patients were cirrhotics and the Child-Pugh score was up to 10 (80% were Child class A and 20% Child class B/C). The virological response after 3 mo of antiviral treatment was 97%. Interestingly, HCV RNA undetectability appeared to occur more rapidly in patients with Child class A, compared to those with Child class B (at week 2: 56% vs 44%; at week 4: 100% vs 75%). No treatment breakthroughs were recorded; dizziness and nausea were the most common adverse events, while low rates of discontinuation were observed due to adverse event. Episodes of ascites, as well as hepatic encephalopathy, declined substantially over time in treated patients.

Gane *et al*^[18] evaluated 20 patients with CHC genotype 1 and Child class B cirrhosis who received ledipasvir/sofosbuvir co-formulation with or without RBV. So far, high SVR rate (89%) with good safety and tolerance and without treatment discontinuations has been reported. Finally, in a study by Flamm *et al*^[19], the same combination of ledipasvir/sofosbuvir plus

RBV (the latter starting from 600 mg/d) was given for 12 or 24 wk in 108 treatment naive or experienced genotype 1 and 4 patients with decompensated cirrhosis Child class B ($n = 55$) or C ($n = 53$)^[19]. All patients had no HCC, well preserved renal function (glomerular filtration rate > 40 mL/min) and total serum bilirubin < 10 mg/dL. The authors found that this combination was well tolerated resulting in high SVR rates irrespectively of duration of antiviral therapy (12 wk: 87%, 24 wk: 89%) and with similar efficacy between Child B and C patients (12 wk: 87% vs 86%, respectively; 24 wk: 89% vs 90%, respectively). Only 4 (4%) patients had serious adverse events.

GUIDANCE FOR THE USE OF IFN-FREE REGIMES IN LIVER TRANSPLANT CANDIDATES

Achievement of undetectable HCV RNA can prevent HCV recurrence post LT. On the other hand, patients with portal hypertension and decompensated

Table 2 Studies of interferon-free regimens for treatment of hepatitis C virus positive liver transplant candidates

Ref.	No. of patients	Severity of liver disease based on CP score	Antiviral scheme (duration)	Virological response
Curry <i>et al</i> ^[16]	61	≤ 7	SOF + RBV (for 48 wk or until LT)	69% (12 wk after LT)
Afdhal <i>et al</i> ^[17]	40	5-10	SOF + RBV (48 wk)	100% and 93% for Child class A and B, respectively at 24 wk under treatment
Gane <i>et al</i> ^[18]	20	7-9	SOF + Ledipasvir ± RBV (12 wk)	89%
Flamm <i>et al</i> ^[19]	108	Decompensated cirrhosis (CP score range: 7-12)	Ledipasvir/SOF + RBV (12 or 24 wk)	87% and 89% (for 12 and 24 wk, respectively)

CP: Child-Pugh; SOF: Sofosbuvir; RBV: Ribavirin.

cirrhosis may not respond equally well with patients with less advanced disease perhaps due to hepatic changes that could affect the DAAs metabolism and pharmacokinetics. It should be noted that the rates of on-therapy virological responses increase more slowly and the final SVR rates are lower in patients with decompensated cirrhosis compared to those in patients with compensated cirrhosis included in the same studies^[17,19,20].

Since not only liver but also renal impairment may be present in patients with decompensated cirrhosis and LT candidates, careful selection of DAAs is required. The agents for this setting should have unchanged pharmacokinetics irrespectively of liver and/or renal dysfunction. Sofosbuvir is cleared through the kidneys and therefore its pharmacokinetic is not affected by the presence of liver impairment^[21]. No dose adjustment of sofosbuvir is required in patients with creatinine clearance ≥ 30 mL/min, but the agent is officially contraindicated in patients with creatinine clearance < 30 mL/min or under hemodialysis^[22]. Recent data suggest that sofosbuvir may have acceptable pharmacokinetic in the latter patient subgroup if it is given at a daily dose of 200 mg. Similarly to sofosbuvir, the combination of ledipasvir/sofosbuvir needs no dose adjustment in patients with any liver impairment or with glomerular filtration rate ≥ 30 mL/min, but it is also contraindicated in cases with glomerular filtration rate < 30 mL/min. Dose adjustment is not needed for any other agent in patients with any degree of liver or renal impairment. However, simeprevir and paritaprevir, as all existing NS3/4 protease inhibitors, are contraindicated in patients with severe liver impairment and Child class C cirrhosis mostly due to safety precautions^[23] (Table 1).

All above data indicate that several factors should be taken into account before the choice of IFN-free regimens in the pre-LT setting. Safe combined regimens with high potency and high genetic barrier should be preferred to achieve rapid inhibition of HCV replication and eliminate the selection risk of resistant-associated viral strains. Given the high efficacy of the new regimens even in LT recipients, a key question is whether all HCV LT candidates require antiviral therapy

before LT. According to reasonable clinical judgment, patients with chances of liver function improvement may be better treated and perhaps avoid the need for LT, but the treatment indication is debatable for patients who will need LT anyway. Since the latter two subgroups cannot be always differentiated, therapeutic decisions are often individualized.

TREATMENT OF HCV LT RECIPIENTS

The efficacy of previous therapeutic options was rather limited in HCV LT recipients, but the availability of the current DAAs has opened a new era in the management of these patients. The optimal timing for onset of treatment with IFN-free regimens in LT recipients has not been determined, but even the current safe DAAs should be used very cautiously in the early post-transplant period due to the potentially unstable clinical and biochemical patients' status, the possible surgical complications and the effect of heavy immunosuppression. Drug-drug interactions should be also taken into account when DAAs are going to be used by LT recipients who often receive several other medications. In particular for calcineurin inhibitors, there are no interactions with sofosbuvir, ledipasvir/sofosbuvir and daclatasvir. Simeprevir should not be given in patients receiving cyclosporine, while the combination of ritonavir boosted paritaprevir/ombitasvir increase the levels of both tacrolimus and cyclosporine which needs to be reduced to 0.5 mg weekly or 0.2 mg every 72 h for tacrolimus and to 20% of the previous dose for cyclosporine (Table 1).

Two studies have evaluated the use of sofosbuvir and RBV in LT recipients with CHC. Initially, sofosbuvir with RBV plus/minus PegIFN was given for 24-48 wk in 104 LT recipients with HCV fibrosing cholestatic hepatitis or decompensated cirrhosis within a compassionate use program^[24]. Sofosbuvir plus RBV (without pegIFN) was given in 80 (77%) patients. Most of the patients had baseline decompensated liver disease with mean bilirubin 3.1 mg/dL and mean albumin 3.1 g/dL. At week 4, 54% of patients had HCV RNA < 25 IU/mL, while 54 (59%) of 92 patients achieved SVR. At the end of follow-up, the clinical condition (defined as liver function improvement and/

Table 3 Studies of sofosbuvir plus simeprevir with or without ribavirin in recipients with hepatitis C recurrence after liver transplantation

Ref.	No. of patients	Patient characteristics	Antiviral Scheme, (duration)	On treatment virological response (%)	SVR (%)
Pungpapong <i>et al</i> ^[28]	55	Fibrosis 3-4: 29%, Decompensated cirrhosis: 4%, Cholestatic recurrence: 15%	SOF + SMV ± RBV (12 wk)	98 (EOT)	91
Brown <i>et al</i> ^[29]	143	Cirrhosis: 60%, MELD score > 10: 14% Previous DAA failure: 9%	SOF + SMV ± RBV (12-24 wk)	-	90
Satokar <i>et al</i> ^[30]	59	Fibrosis F3/F4: 51%, Treatment experience: 71%	SOF + SMV SOF + SMV + RBV SOF + RBV	62 50 43 (4 wk)	-
Gordon <i>et al</i> ^[31]	17	Fibrosis: range: 0-4	SOF + SMV (12 wk)	100 (EOT)	-
Gutierrez <i>et al</i> ^[32]	32	-	SOF + SMV ± RBV (12 wk)	93 (EOI)	-
Punzalan <i>et al</i> ^[37]	10	Median Fibrosis: 2.5, Treatment experience: 40%	SOF + SMV ± RBV (12 wk)	100 (EOT)	100
Lutchman <i>et al</i> ^[33]	41	Treatment experience: 56%	SOF + SMV or SOF + RBV (12-24 wk)	100 (8 wk)	-
Nair <i>et al</i> ^[34]	22	All patients with fibrosis ≥ 3 or decompensated cirrhosis	SOF + SMV ± RBV (12 wk)	100 (EOT)	-
Ripper <i>et al</i> ^[35]	25	Treatment experience: 64%	SOF + SMV ± RBV (12 wk)	100 (8 wk)	75
O'Dell <i>et al</i> ^[38]	16	-	SOF + SMV ± RBV	100 EOT	100
Alsabbagh <i>et al</i> ^[36]	17	Fibrosis F3-4: 40%, Treatment experience: 41%	SOF + SMV (n = 11) SOF + RBV (n = 6) (24 wk)	100 (4 wk)	-

EOT: End of treatment; CTP: Child-Pugh score; DAA: Direct acting antiviral.

or reduction of decompensation episodes) improved in 59 (57%) and remained stable in 23 (22%) cases. Serious adverse events including ascites, diabetes, neutropenia, hemophagocytic syndrome and bone marrow aplasia, which were usually not related to the study drugs, were noted in 5% of patients and resulted in early treatment discontinuation in 6 patients. Similarly encouraging were reported in two patients with fibrosing cholestatic hepatitis (with genotype 4 and 1a, respectively)^[25,26] who were successfully treated with sofosbuvir plus RBV.

In the second open-label study^[27], 40 liver transplant recipients with HCV recurrence of any genotype were enrolled 24 wk after LT. Forty percent of the patients had cirrhosis, but none liver decompensation. They were all treated for up to 6 mo with sofosbuvir plus RBV (the latter starting from 400 mg per day). All patients achieved undetectable HCV-RNA by week 4 under treatment, while the SVR rate 4 wk after the end of antiviral therapy was 77% (27/35). No graft dysfunction was recorded and no adjustments of immunosuppressive regimen were needed. Serious adverse events occurred in 15% of patients but they were all unrelated to the study drug. Common side events included fatigue, arthralgia, diarrhea and mild to moderate anemia and occurred in 18% of patients.

The combinations of sofosbuvir with other DAAs have shown excellent SVR rates without serious

adverse effects in LT recipients, including prior difficult to treat subgroups such as patients with genotype 1, cirrhosis, previous intolerance or non-response to IFN therapy. The combination of sofosbuvir with simeprevir plus/minus RBV given for 3 mo showed high efficacy in 55 LT recipients with HCV recurrence (advanced fibrosis or cirrhosis: 29%, cholestatic hepatitis: 11%). SVR was observed in 96% of patients with mild to moderate fibrosis and 76% of patients with advanced fibrosis or cirrhosis^[28]. Similarly, 90% SVR was observed in the multicenter HCV-TARGET study^[29], in which 143 genotype 1-3 LT recipients received sofosbuvir plus simeprevir with or without RBV (60% had cirrhosis, 14% had MELD score > 10 and 9% failure to regimens with a first-generation protease inhibitor). SVR rate was higher in patients without cirrhosis (94% vs 86%), with MELD score < 10 (92% vs 77%) or with genotype 1b (95% vs 83%). In both studies, only mild to moderate adverse events including fatigue, anemia and headache were recorded^[28,29]. Finally, sofosbuvir combination with simeprevir with or without RBV have shown good on treatment safety and efficacy in series or small cohort studies, but most of them lack SVR data yet^[30-38] (Table 3).

The effectiveness of ledipasvir with sofosbuvir plus RBV for 12 or 24 wk was assessed in 223 recipients with HCV genotype 1 or 4. Of these patients, 111

Table 4 Studies of sofosbuvir plus daclatasvir with or without ribavirin in recipients with hepatitis C recurrence after liver transplantation

Authors	No. of patients	Patient characteristics	Antiviral Scheme (duration)	On treatment virological response (%)	SVR (%)
Leroy <i>et al</i> ^[39] , (CUPILT study)	21	FCH: 100%, Treatment experience: 67%	SOF + Daclatasvir ± RBV (<i>n</i> = 13) SOF + RBV (<i>n</i> = 6) (24 wk)	95 (12 wk)	-
Conti <i>et al</i> ^[40]	55	Fibrosis F3-F4: 33%, FCH: 7%	SOF + Daclatasvir (24 wk)	85 (8 wk)	-

FCH: Fibrosing cholestatic hepatitis.

Table 5 Main strategies of interferon-free antiviral combinations in liver transplant candidates and recipients with chronic hepatitis C virus infection

Antiviral scheme (duration)	Antiviral activity
SOF + RBV (× 12 or 24 wk)	Genotype 2 or 3 (perhaps 5, 6)
SOF + Simeprevir ± RBV (× 12 or 24 wk)	Genotypes 1, 4
SOF + Daclatasvir ± RBV (× 12 or 24 wk)	Genotypes 1, 3, 4
Ledipasvir/SOF ± RBV (× 12-24 wk)	Genotypes 1, 3, 4, 6
Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir ± RBV (× 12 or 24 wk)	Genotype 1
Paritaprevir/Ritonavir/Ombitasvir ± RBV (× 12 or 24 wk)	Genotype 4

SOF: Sofosbuvir; RBV: Ribavirin.

were non-cirrhotics, while 51, 52 and 9 cases had Child class A, B, and C cirrhosis, respectively. SVR rates were higher in non-cirrhotics (96%-98%) and patients with Child class A cirrhosis (96%) compared to patients with Child class B (83%-85%) or Child class C cirrhosis (60%-67%). However, there was no significant difference between the 12-wk and 24-wk treatment arms in each patient subgroup^[20]. Similarly, the combination of sofosbuvir plus daclatasvir with or without RBV showed good safety and efficacy in LT recipients with advanced liver disease or severe fibrosing cholestatic recurrence from HCV genotype 1-4 in small cohort studies^[39,40] (Table 4).

In a phase II study, the combination of paritaprevir/ombitasvir plus dasabuvir plus RBV given for 24 wk was evaluated in 34 LT recipients with CHC genotype 1 and mild to moderate fibrosis (11% with cholestatic recurrence). All but one patient (97%) achieved SVR. Immunosuppression dosing was easily manageable over the study period by reducing cyclosporine at 20% of the pretreatment total daily dose and tacrolimus at 0.5 mg once weekly. No graft loss or episode of rejection was recorded with these modifications. In addition, the regimen was generally well tolerated with only one patient discontinuing the study due to skin rash and anxiety.

CONCLUSION

The recent progress in the management of CHC has been outstanding with the benefits being particularly evident in the treatment of patients with advanced disease^[41]. In contrast to the pre-DAA era, both LT candidates and recipients can now be safely and effectively treated (Table 5). Although the high cost

of the available DAAs raises discussions and public health debates about their priorities and optimal use worldwide, there is no controversy on the use of the IFN-free regimens in LT candidates and recipients. The most important remaining clinical dilemma remains the need for therapeutic intervention in LT candidates with very advanced liver disease, mostly Child class C cirrhosis. Given the possible complications and the frequent use of other medications, the therapeutic regimens should be carefully selected in this setting. HCV genotype, liver and renal function and co-medications should be always taken into account.

REFERENCES

- 1 **Lavanchy D.** The global burden of hepatitis C. *Liver Int* 2009; **29** Suppl 1: 74-81 [PMID: 19207969 DOI: 10.1111/j.1478-3231.2008.01934.x]
- 2 **Alter MJ.** Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 2007; **13**: 2436-2441 [PMID: 17552026 DOI: 10.3748/wjg.v13.i17.2436]
- 3 **Maasoumy B, Wedemeyer H.** Natural history of acute and chronic hepatitis C. *Best Pract Res Clin Gastroenterol* 2012; **26**: 401-412 [PMID: 23199500 DOI: 10.1016/j.bpg.2012.09.009]
- 4 **Terrault N.** Liver transplantation in the setting of chronic HCV. *Best Pract Res Clin Gastroenterol* 2012; **26**: 531-548 [PMID: 23199510 DOI: 10.1016/j.bpg.2012.09.010]
- 5 **Alexopoulou A, Papatheodoridis GV.** Current progress in the treatment of chronic hepatitis C. *World J Gastroenterol* 2012; **18**: 6060-6069 [PMID: 23155334 DOI: 10.3748/wjg.v18.i42.6060]
- 6 **Papatheodoridis GV, Cholongitas E.** Chronic hepatitis C and no response to antiviral therapy: potential current and future therapeutic options. *J Viral Hepat* 2004; **11**: 287-296 [PMID: 15230850 DOI: 10.1111/j.1365-2893.2004.00522.x]
- 7 **Cholongitas E, Papatheodoridis GV.** Review article: novel therapeutic options for chronic hepatitis C. *Aliment Pharmacol Ther* 2008; **27**: 866-884 [PMID: 18284651 DOI: 10.1111/j.1365-2036.2008.03644.x]
- 8 **Hézode C, Fontaine H, Dorival C, Zoulim F, Larrey D, Canva**

- V, De Ledinghen V, Poynard T, Samuel D, Bourliere M, Alric L, Raabe JJ, Zarski JP, Marcellin P, Riachi G, Bernard PH, Loustaud-Ratti V, Chazouilleres O, Abergel A, Guyader D, Metivier S, Tran A, Di Martino V, Causse X, Dao T, Lucidarme D, Portal I, Cacoub P, Gournay J, Grando-Lemaire V, Hillon P, Attali P, Fontanges T, Rosa I, Petrov-Sanchez V, Barthe Y, Pawlowsky JM, Pol S, Carrat F, Bronowicki JP. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. *Gastroenterology* 2014; **147**: 132-142.e4 [PMID: 24704719 DOI: 10.1053/j.gastro.2014.03.051]
- 9 **Herbst DA**, Reddy KR. Sofosbuvir, a nucleotide polymerase inhibitor, for the treatment of chronic hepatitis C virus infection. *Expert Opin Investig Drugs* 2013; **22**: 527-536 [PMID: 23448131 DOI: 10.1517/13543784.2013.775246]
- 10 **Hayashi N**, Seto C, Kato M, Komada Y, Goto S. Once-daily simeprevir (TMC435) with peginterferon/ribavirin for treatment-naïve hepatitis C genotype 1-infected patients in Japan: the DRAGON study. *J Gastroenterol* 2014; **49**: 138-147 [PMID: 24005956 DOI: 10.1007/s00535-013-0875-1]
- 11 **Kumada H**, Suzuki Y, Ikeda K, Toyota J, Karino Y, Chayama K, Kawakami Y, Ido A, Yamamoto K, Takaguchi K, Izumi N, Koike K, Takehara T, Kawada N, Sata M, Miyagoshi H, Eley T, McPhee F, Damokosh A, Ishikawa H, Hughes E. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. *Hepatology* 2014; **59**: 2083-2091 [PMID: 24604476 DOI: 10.1002/hep.27113]
- 12 **Gentile I**, Borgia F, Coppola N, Buonomo AR, Castaldo G, Borgia G. Daclatasvir: the first of a new class of drugs targeted against hepatitis C virus NS5A. *Curr Med Chem* 2014; **21**: 1391-1404 [PMID: 24372205 DOI: 10.2174/0929867321666131228222215]
- 13 **Klibanov OM**, Gale SE, Santevecchi B. Ombitasvir/paritaprevir/ritonavir and dasabuvir tablets for hepatitis C virus genotype 1 infection. *Ann Pharmacother* 2015; **49**: 566-581 [PMID: 25680759 DOI: 10.1177/1060028015570729]
- 14 **Wiesner RH**, Sorrell M, Villamil F. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. *Liver Transpl* 2003; **9**: S1-S9 [PMID: 14586888 DOI: 10.1053/jlts.2003.50268]
- 15 **Roche B**, Samuel D. Hepatitis C virus treatment pre- and post-liver transplantation. *Liver Int* 2012; **32** Suppl 1: 120-128 [PMID: 22212582 DOI: 10.1111/j.1478-3231.2011.02714.x]
- 16 **Curry MP**, Fornis X, Chung RT, Terrault NA, Brown R, Fenkel JM, Gordon F, O'Leary J, Kuo A, Schiano T, Everson G, Schiff E, Befeler A, Gane E, Saab S, McHutchison JG, Subramanian GM, Symonds WT, Denning J, McNair L, Arterburn S, Svarovskaia E, Moonka D, Afdhal N. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. *Gastroenterology* 2015; **148**: 100-107.e1 [PMID: 25261839 DOI: 10.1053/j.gastro.2014.09.023]
- 17 **Afdhal N**, Everson G, Calleja J. Sofosbuvir and ribavirin for the treatment of chronic hepatitis C with cirrhosis and portal hypertension with or without decompensation: early virologic response and safety. *J Hepatol* 2014; **60**: S23 [DOI: 10.1016/S0168-8278(14)60070-2]
- 18 **Gane E**, Hyland R, An D, Pang P, Symonds W, McHutchison J, Stedman C. Sofosbuvir/Ledipasvir fixed dose combination is safe and effective in difficult-to-treat populations including genotype-3 patients, decompensated type 3 patients and genotype 1 patients with prior sofosbuvir treatment experience. *J Hepatol* 2014; **60**: S21-S22 [DOI: 10.1016/S0168-8278(14)60008-8]
- 19 **Flamm S**, Everson GT, Charlton M, Denning J, Arterbur S, Brandt-Sarif S, Pang P, McHutchison J, Reddy K, Afdhal N. Ledipasvir/Sofosbuvir with Ribavirin for the treatment of HCV in Patients with Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter study. *Hepatology* 2014; **60** (Suppl 4): 321A.
- 20 **Reddy KR**, Everson G, Flamm S. Ledipasvir/Sofosbuvir with Ribavirin for the Treatment of HCV in Patients with Post Transplant Recurrence: Preliminary Results of a Prospective, Multicenter Study. *Hepatology* 2014; **60** (Suppl 4): 200A
- 21 **Kirby B**, Gordi T, Symonds W, Kearney B, Mathias A. Population pharmacokinetics of sofosbuvir and its major metabolite (GS-331007) in healthy and HCV infected adult subjects. *Hepatology* 2013; **58** (Suppl 4): 746A
- 22 **Alverlind S**, Barassin S, Dalén P, Li Y, Toler S, Eriksson H, Tummala R. Clinical pharmacokinetics of the nicotinic channel modulator dexmecamylamine (TC-5214) in subjects with various degrees of renal impairment. *Clin Drug Investig* 2014; **34**: 457-465 [PMID: 24760402 DOI: 10.1016/S0168-8278(12)61113-1]
- 23 **Lens S**, Gambato M, Londoño MC, Fornis X. Interferon-free regimens in the liver-transplant setting. *Semin Liver Dis* 2014; **34**: 58-71 [PMID: 24782259 DOI: 10.1055/s-0034-1371011]
- 24 **Fornis X**, Charlton M, Denning J, McHutchison JG, Symonds WT, Brainard D, Brandt-Sarif T, Chang P, Kivett V, Castells L, Prieto M, Fontana RJ, Baumert TF, Coilly A, Londoño MC, Habersetzer F. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. *Hepatology* 2015; **61**: 1485-1494 [PMID: 25557906 DOI: 10.1002/hep.27681]
- 25 **Borentain P**, Colson P, Dhiver C, Gregoire E, Hardwigsen J, Botta-Fridlund D, Garcia S, Gerolami R. Successful treatment with sofosbuvir of fibrosing cholestatic hepatitis C after liver transplantation in an HIV-HCV-coinfected patient. *Antivir Ther* 2015; **20**: 353-356 [PMID: 25105441 DOI: 10.3851/IMP2841]
- 26 **Kim B**, Trivedi A, Thung SN, Grewal P. Case report of successful treatment of fibrosing cholestatic hepatitis C with sofosbuvir and ribavirin after liver transplantation. *Semin Liver Dis* 2014; **34**: 108-112 [PMID: 24782264 DOI: 10.1055/s-0034-1371084]
- 27 **Samuel D**, Charlton E, Gane E, Brown J, Curry M, Kwo P, Fontana R, Gilroy R, Teperman L, Muir A. Sofosbuvir plus ribavirin for the treatment of recurrent hepatitis C infection after liver transplantation: Results of a prospective, multicenter study. *J Hepatology* 2014; **60**: S499 [DOI: 10.1016/S0168-8278(14)61392-1]
- 28 **Pungpapong S**, Aqel B, Leise M, Werner KT, Murphy JL, Henry TM, Ryland K, Chervenak AE, Watt KD, Vargas HE, Keaveny AP. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. *Hepatology* 2015; **61**: 1880-1886 [PMID: 25722203]
- 29 **Brown R**, Reddy KR, O'Leary J, Kuo A, Morelly G, Stravitz R, Durand C, Di Bisceglie AM. Safety and efficacy of new DAA based therapy for hepatitis C post-transplant: interval results from the HCV-TARGET longitudinal observational study. *Hepatology* 2014; **60** (Suppl 1): LB-4
- 30 **Satokar R**, Ahn J, Te H, Deising A, Aronsohn A, Robertazzi S, Schiano T. Sofosbuvir as the backbone of treatment for HCV after liver transplantation: a real-life multicenter experience. *Hepatology* 2014; **60** (Suppl 1): 537A
- 31 **Gordon F**, Kosinski A, Coombs S, Goucher P, Aljahdli E, Pomfret E. Sofosbuvir Simeprevir is Safe in Liver Transplant Recipients. *Hepatology* 2014; **60** (Suppl 1): 543A
- 32 **Gutierrez J**, Grigorian A, Carion A, Schweitzer M, Avalos D, Bhamidimarri K, Peyton A. Safety and Efficacy of Hepatitis C Therapy with Sofosbuvir and Simeprevir after Liver Transplantation. *Hepatology* 2014; **60** (Suppl 1): 545A
- 33 **Lutchman G**, Nguyen N, Hsiao T, Vu VD, Chen V, Ahmed A, Daugherty T, Garcia G, Kumari R, Kim WR, Nguyen M. Safety and Effectiveness of Sofosbuvir (SOF) in Combination with Simeprevir (SIM) or Ribavirin (RBV) for the Treatment of Hepatitis C Virus (HCV) Recurrence after Liver Transplant (LT). *Hepatology* 2014; **60** (Suppl 1): 670A
- 34 **Gutierrez JA**, Carrion AF, Avalos D, O'Brien C, Martin P, Bhamidimarri KR, Peyton A. Sofosbuvir and simeprevir for treatment of hepatitis C virus infection in liver transplant recipients. *Liver Transpl* 2015; **21**: 823-830 [PMID: 25825070]
- 35 **Ripper S**, Holt EW, Cooper S, Wakil A, Davern T, Merriman R, Guy J, Todd Frederik R. Simeprevir plus Sofosbuvir for Patients with Recurrence of Genotype 1 Hepatitis C Infection after Liver Transplantation. *Hepatology* 2014; **60** (Suppl 1): 684A
- 36 **Alsabbagh M**, Hanouneh I, John BV, Guirguis J, Eghtesad B, Fung J, Zein N, Alkhouri N. Safety and efficacy of all-oral sofosbuvir-based regimens to treat HCV recurrence post-liver transplantation.

- Hepatology* 2014; **60** (Suppl 1): 700A
- 37 **Punzalan C**, Zacharias I, Rodrigues J, Mehta S, Bozorgzadeh A, Barnad G. Successful treatment of post liver transplant patients with genotype 1 hepatitis C virus with sofosbuvir and simeprevir. *Hepatology* 2014; **60** (Suppl 1): 688A
- 38 **O'Dell H**, Raiford D, Scanga A, Chung C, Perri R. Combination Sofosbuvir and Simeprevir is Very Effective and Well Tolerated for the Treatment of Recurrent Hepatitis C after Liver Transplant. *Hepatology* 2014; **60** (Suppl 1): LB-4
- 39 **Leroy V**, Dumortier J, Coily A, Sebah M, Fougere-Leurent C, Radenne S, Botta D, Durand F, Silvain C, Lebray P, Housset-Debry P, Kamar N, d'Alteroche L, Calmus Y, Bertucci I, Pageaux GP, Duclos-Vallee J. High rates of virological response and major clinical improvement during sofosbuvir and daclatasvir-based regimens for the treatment of fibrosing cholestatic HCV-recurrence after liver transplantation: The ANRS CO23 CUPILT study. *Hepatology* 2014; **60** (Suppl 1): 207A
- 40 **Conti F**, Lebray P, Schielke A, Regnault H, Thabut D, Eyraud D, Pouljol-Robert A, Chazouilhres O, Calmus Y. Sofosbuvir/Daclatasvir Therapy for Recurrent Hepatitis C after Liver Transplantation: Preliminary report from the parisian centers. *Hepatology* 2014; **60** (Suppl 1): 208A
- 41 **Dall'Agata M**, Gramenzi A, Biselli M, Bernardi M. Hepatitis C virus reinfection after liver transplantation: is there a role for direct antiviral agents? *World J Gastroenterol* 2014; **20**: 9253-9260 [PMID: 25071318]

P- Reviewer: Georgopoulou U, Kim SR, Labonte P **S- Editor:** Ma YJ
L- Editor: A **E- Editor:** Zhang DN





Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>
<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045