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TOPIC HIGHLIGHT

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Management of hepatitis C infection before and after liver transplantation

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Abstract

Chronic hepatitis C (CHC) is the most common indication for liver transplantation (LT). Aggressive treatment of hepatitis C virus (HCV) infection before cirrhosis development or decompensation may reduce LT need and risk of HCV recurrence post-LT. Factors associated with increased HCV risk or severity of recurrence include older age, immunosuppression, HCV genotype 1 and high viral load at LT. HCV recurrence post-LT leads to accelerated liver disease and cirrhosis development with reduced graft and patient survival. Currently, interferon (IFN)-based regimens can be used in dual-agent regimens with ribavirin, in triple-agent antiviral strategies with direct-acting antivirals (*e.g.*, protease inhibitors telaprevir or boceprevir), or before transplant in compensated patients to reduce HCV viral load to prevent or reduce the risk of post-LT recurrence and complications; they cannot be used in patients with decompensated cirrhosis. IFN-based regimens are used in less than half of HCV-infected patients waiting for LT due to extremely low efficacy and poor tolerability. However, antiviral therapy is indicated after LT in patients with histologically confirmed CHC despite tolerability issues. Improvements in side effect management have increased survival in patients achieving therapeutic targets. HCV treatment pre- and post-LT results in significant health care costs especially when lack of efficacy leads to disease worsening, although studies have shown sofosbuvir treatment before LT *vs* conventional post-LT dual antiviral is cost effective. The suboptimal efficacy and tolerability of IFN-based therapies, plus the significant economic burden, means the need for effective and well tolerated IFN-free anti-HCV therapy for pre- and post-LT remains high.

Key words: Hepatitis C virus; Orthotopic liver trans-

plantation; Interferon-free treatment; Decompensated cirrhosis; Chronic hepatitis C

Core tip: This paper discusses alternative treatment options for patients with hepatitis C virus (HCV) undergoing liver transplantation (LT), particularly those with decompensated cirrhosis in whom interferon (IFN)-based therapy is contraindicated. Virtually all patients undergoing LT experience HCV recurrence leading to accelerated liver disease and cirrhosis development with reduced graft and patient survival. Novel IFN-free antiviral therapies featuring better efficacy and tolerability in such patients shall increase sustained virologic response rates while decreasing side effects and drug interactions, thus preventing progression of HCV-related liver disease, decreasing the general costs associated with both HCV treatment and worsening of patient health.

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INTRODUCTION

In Europe, approximately 8 million people are infected with hepatitis C virus (HCV)[1]. Untreated chronic hepatitis C (CHC) leading to cirrhosis, and, ultimately, end-stage liver disease (ESLD), is the most common indication for orthotopic liver transplantation (LT); CHC accounts for approximately 28%-40% of all LTs according to 2011 United States data[2]. In Italy, HCV-related ESLD accounts for 30%-40% of LTs[3].

HCV infection recurs virtually universally after LT and histologically documented CHC develops in approximately 70% of patients during the first year after LT[4]. Factors associated with increased risk and/or severity of HCV infection recurrence include donor and recipient age, quality of the graft, immunosuppression, HCV and *IL28B* genotypes, viral load, and cytomegalovirus infection[1,5]. Aggressive HCV treatment before development of cirrhosis or hepatic decompensation can prevent the need for transplantation or reduce the risk of post-LT recurrence[1,5,6]. HCV recurrence post-LT can lead to accelerated liver disease: 20%-30% of patients with recurrent HCV develop cirrhosis in the graft liver within 5 years, with significantly reduced allograft and patient survival[7,8].

At present, interferon (IFN)-based regimens are contraindicated in many patients with cirrhosis and in all with decompensated disease[9]. IFN-based HCV treatment after LT is poorly tolerated due to severe side effects (particularly anemia and infections) resulting in poor outcomes[6]. Hence, while major advances have been seen in the treatment of CHC in immunocompetent patients, outcomes in immunosuppressed LT recipients are still far from optimal[6], and the need for effective and well tolerated anti-HCV therapy both pre- and post-LT remains high.

This narrative review examines the clinical approach, efficacy, tolerability and pharamacoeconimcs of antiviral therapy, as well as novel therapies, in patients with CHC in the LT setting.

Methodology

Papers included in this narrative review were identified by an electronic search of PubMed; search terms included "hepatitis C virus", "cirrhosis", "liver transplantation", "hepatic transplantation" and "interferon-free treatment". Relevant studies (those relating to human subjects) were then selected from the results, and from bibliographies of relevant reviews and the author's own experience. For the purposes of this review, the results from the literature search were group into 8 sections/discussion points: (1) patient screening/eligibility; (2) response to therapy and mortality; (3) efficacy of therapy; (4) tolerability; (5) novel therapies; (6) pharmacoeconomics of treatment; and (7) conclusions.

ELIGIBILITY FOR ANTIVIRAL THERAPY

The most reliable way to prevent post-transplantation HCV-recurrence is to cure the infection before LT. Unfortunately antiviral therapy is not feasible in approximately half of HCV infected patients requiring LT, due to the contraindications mentioned above[1,10]. In addition, sustained virologic response (SVR) rates are typically lower in cirrhotic patients, especially in those infected by genotype-1 HCV.

Therefore, patients must be carefully selected for IFN-based treatment. Patients eligible for antiviral therapy prior to LT include those with maintained liver function (Child-Pugh A cirrhosis) and some with Child-Pugh stage B cirrhosis (albumin > 3.5 g/dL and > 100000/mm^3 platelets[11,12] who have predictors of good response[1]. In these patients, treatment should be started promptly, with the aim of achieving SVR to avoid LT or post-LT HCV recurrence[1].

Until 2011, dual IFN-based therapy such as pegylated interferon alpha (PEG-IFNα) plus ribavirin (RBV) was standard HCV treatment for all patients. Since the introduction in 2011 of the first two direct-acting antiviral agents (DAAs), the protease inhibitors (PIs) telaprevir (TVR) and boceprevir (BOC), triple therapy (TVR or BOC plus PEG-IFN plus RBV) has become standard treatment in eligible patients with HCV genotype 1 infection[1].

Reviews on first generation PIs used in the pre- and post-transplant setting reported higher SVR rates *vs*

PEG-IFN/RBV even in patients with advanced disease. However, side effects and drug-drug interactions will possibly hamper and limit their use in both transplant scenarios; thus, a careful selection and monitoring of patients will be crucial[13,14].

RELATIONSHIP BETWEEN ANTI-HCV THERAPY RESPONSE AND MORTALITY

SVR is the most widely accepted indication of clinical response in HCV infection and offers a surrogate marker of cure. SVR can be achieved as early as 12 wk after the start of treatment. However, the gold standard definition worldwide is the absence of detectable HCV-RNA in the serum after 24 wk from the end of treatment (EOT)[1]. In patients awaiting LT, achieving SVR reduces the risk of graft reinfection and consequently is predictive of a reduced risk of retransplantation[1]. The relationship between SVR and reduced liver-related mortality rate in LT has been shown in several studies[15-17]. A meta-analysis showed that achieving SVR is associated with substantially lower liver-related morbidity and mortality (RR = 0.23; 95%CI: 0.10-0.52)[16]. The risk of HCC and hepatic decompensation is also lower in patients achieving an SVR *vs* those who have failed treatment[15,16]. In a large long-term mortality study in 530 patients with CHC and advanced fibrosis receiving IFN-based treatment, 36% achieved an SVR and the 10-year cumulative all-cause mortality rate was 8.9% in patients with SVR and 26.0% in those without ($P < 0.001$; HR = 0.26; 95%CI: 0.14-0.49)[17].

EFFICACY OF ANTIVIRAL THERAPY IN THE LT SETTING

Due to a wide range of demographic, disease-related, genetic and treatment-related factors, response rates with anti-HCV treatment vary enormously in the pre- and post-LT setting[1].

Duration of current antiviral therapy

Selecting the appropriate duration of treatment in a single patient for the achievement of SVR is a crucial issue and it is guided mainly by liver disease severity, the viral genotype, and on-treatment early virologic responses (EVRs; weeks 4 and 12)[1].

Host polymorphisms located upstream of the *IL28B* gene are associated with a high chance of rapid virological response (RVR) and SVR with PEG-IFNα/RBV in HCV genotype 1-infected patients. Genotyping of IL-28B polymorphisms may be useful for predicting treatment outcome as well as estimating the optimal duration of PEG-IFN/RBV combination therapy for viral eradication; patients with a favorable IL28B genotype receiving treatment for a standard duration, and those with an unfavorable genotype receiving treatment for ⩾ 48 wk[18]. However, extending treatment to beyond 48 wk might be a concern due to tolerability issues, with higher treatment discontinuation rates reported[19-21]. Furthermore, in the LT setting, many patients do not achieve an SVR even with 48 wk' treatment. More effective agents would allow shorter treatment regimens.

Pre-LT antiviral therapy

Pre-LT antiviral therapy reduces the risk of post-LT HCV recurrence[5]. All patients with detectable HCV at the time of transplantation will develop an infection post-transplant, leading to CHC in most patients and cirrhosis in 5%-30% and progressive graft failure and death at 3 years in 27% and 34%, respectively[10,22-24]. Therefore, virus eradication or an undetectable HCV viral load before LT dramatically improves patient prognosis[1,5,7]. Unfortunately, patients with progressive CHC needing LT often have other factors associated with poor or slow response to IFN-based treatment (*e.g.*, older age, male gender, chronic alcohol consumption, obesity, type 2 diabetes and immunosuppression, hypersplenism) and worse tolerance to therapy[1].

A study evaluating the efficacy of IFNα-2b 3 MU/d and RBV 800 mg/d to prevent HCV recurrence in 30 HCV-cirrhotic patients awaiting LT showed an SVR in 9 patients (30%) and non-response in 21. A viral load decrease ⩾ 2 log at week 4 was the strongest predictor of virological response. Of the nine responders who underwent LT, six remained free of infection at median 46-wk follow-up[9].

In another study which evaluated the effectiveness, tolerability, and outcome of a low accelerating dose regimen of antiviral therapy in the treatment of patients with advanced HCV (63% with cirrhosis, mean Child-Pugh score 7.4 ± 2.3), 46% were HCV RNA-negative at EOT and the SVR rate was 24% (13% and 50% in genotype 1 and non-1; $P < 0.0001$[25]. In a long-term follow-up, 12/15 (80%) of those with undetectable HCV-RNA before transplantation remained HCV-negative ⩾ 6 mo or post-LT[25]. In a randomized controlled trial in 79 HCV-infected patients waiting for LT, 59 received PEG-IFN/RBV initiated at 0.75 μg/kg per week per 600 mg/d and escalated to the maximal tolerated dose, and 20 were untreated controls[26]. The combined virologic response [CVR; pre-LT SVR and post-LT virologic response (pTVR)] rates in the intent-to-treat analysis were 19% in the treated group and 6% for control ($P = 0.29$). The difference was significant in the per protocol analysis (22% *vs* 0%, $P = 0.03$) and the pTVR rate increased with treatment duration ($P = 0.01$)[26].

Currently, there are no published studies on the use of PI-based regimens TVR and BOC in patients with very advanced liver disease prior to LT[1].

A small study presented in abstract form at EASL 2014, showed that unspecified triple therapy in

selected HCV-cirrhotic patients on the LT waiting list prevented re-infection post-LT in 7 of 8 patients and none developed rejection[27].

Post-LT antiviral therapy

There is a lack of consensus as to when antiviral therapy should be initiated following transplantation. There are three common approaches to treat HCV-recurrence after LT: (1) pre-emptive treatment given to all patients at or immediately after LT; (2) early treatment of acute hepatitis; and (3) and treatment of established CHC[3,28-30]. Since only 30% of patients will progress to cirrhosis, the pre-emptive approach is unjustified in the majority of patients and too risky for critical patients; therefore, this approach is not recommended. Some studies suggest that early treatment of acute hepatitis is a safe approach resulting in one third of patients achieving an SVR[28], while studies investigating treatment response in established hepatitis show SVR rates from 21%-67%[30].

Identification of predictive factors for cirrhosis

After LT, the amount of necroinflammatory activity in the transplanted organ, as well as the degree of fibrosis at 12 mo, are predictors of poor outcomes; necroinflammation being predictive of eventual cirrhosis, and fibrosis score of $\geqslant$ 2 being predictive of death[31,32]. Severe aggressive HCV infection can occur within 6 mo of LT and is associated with a rapid progression to graft failure[7,23,31,32].

Dual therapy

Standard anti-HCV therapy in post-LT patients with HCV genotype 2/3 (dual PEG-IFN/RBV therapy, for 24-72 wk) has been shown to provide SVR in 30%-60% of patients depending primarily on population and treatment duration[33,34].

In a cohort study of 30 consecutive patients (77% genotype 1) with post-LT HCV recurrence, treated with 48 wk' PEG-IFNα2a 180 μg/wk plus RBV 10 mg/kg per day regardless of genotype, and immunosuppression with a calcineurin inhibitor [tacrolimus (TAC) or cyclosporine (CyA)] and corticosteroid ± mycophenolate mofetil, 19 patients completed 48 wk of treatment. EOT virologic response was 73% and SVR was 60%[33]. This was substantially higher than the 33% SVR rate seen in another cohort study of dual PEG-IFN 0.8-1.6 μg/kg per week plus RBV 800-1200 mg/d in 16 patients with post-LT recurrent HCV. In 12 out of 16 patients completing the full 12 mo treatment, 4 achieved an SVR and had stable or improved liver disease grading and staging scores[34].

Studies have reported improved SVR in post-LT CHC patients failing PEG-IFN-alpha2b and switched to PEG-IFN-α2a-based therapy[35]; but *de novo* autoimmune hepatitis has also been reported with this switch of therapy[36].

Triple therapy regimens

Triple therapy is recommended in patients with histologically proven CHC and HCV genotype 1[1]. Studies and case reports of triple therapy are summarized in Table 1. Of note, treatment durations were generally shorter than for dual therapy but many of the studies and case reports did not report SVR rates.

In a cohort study of LT recipients with HCV recurrence, 12 wk' BOC or TVR therapy, an SVR12 (undetectable HCV RNA 12 wk after EOT) was achieved in 71% (5/7) and 20% (1/5), with BOC and TVR, respectively (P = 0.24). Increased risk of anemia, drug-drug interactions and infections require close monitoring[37].

TVR and BOC-based therapy

A 12-wk pilot study showed that TVR-based triple therapy was effective in post-LT patients with HCV genotype 1[38]. TVR/PEG-IFN/RBV therapy, plus immunosuppressive therapy, was effective within 4-12 wk in 8/9 patients and drug interactions and adverse events (AEs) were managed adequately[38]. In a retrospective follow-up study, 5/9 patients completed the full 48 wk' therapy and five achieved SVR (including one patient who received < 48 wk treatment); management of drug-drug interactions and severe AEs was challenging, but feasible[38].

TVR has been used successfully for post-LT HCV treatment in combination with PEG-IFNα/RBV[39-43], and with TAC[44]. In a case series of 12 post-LT patients with HCV genotype 1 receiving CyA, TVR/PEG-IFN/RBV was effective and safe; the main AE, anemia, was manageable[39]. Two post-LT studies in patients with recurrent HCV genotype 1 showed that TVR triple therapy was effective and well tolerated in the majority of patients used with CyA (n = 7)[42] and with TAC and everolimus (n = 6)[40]. A case report also showed that TVR/TAC + PEG-IFN/RBV in two patients post-LT, one with cholestatic hepatitis and one with aggressive HCV recurrence (genotypes not reported) was safe with careful monitoring and tacrolimus dose adjustment[44].

Recent interim data from the telaprevir phase 3 replace study in treatment-naive stable LT patients with HCV genotype 1, showed TVR/PEG-INF/RBV resulted in an SVR12 in 19 of 32 patients (59.6%)[41] .

In a retrospective analysis of data from 14 HCV G1 patients treated for HCV recurrence after LT with TVR/PEG-IFN/RBV triple therapy [mean treatment duration 47 (2-168) mo], 35.7% (5/14) achieved SVR 24 but severe side effects were common with four patients discontinuing therapy due to infections (n = 2), hematologic side effects (n = 1) and intolerance (n = 1)[27].

PI-based triple therapies have also been used successfully in HCV/HIV co-infected patients with HCV recurrence after LT. In a small study TVR or BOC-based triple therapy, 2 of 7 patients achieved an SVR24, side effects (most commonly anemia) and drug interactions

Table 1 Summary of clinical studies of triple therapy for recurrent hepatitis C virus infection before and after liver transplantation

Study	*n*	Design	Treatment	Duration	Genotype	Immuno-suppressant	Efficacy	Tolerability	Other
Before liver transplantation									
Curry *et al*[56]	61	OL study	SOF (400 mg)/RBV	48 wk	1 (*n* = 45) 2 (*n* = 8) 3 (*n* = 11) 4 (*n* = 1)	PRED TAC MMF	pTVR12: 70%	2 pts discontinued due to AE (pneumonitis, sepsis/acute renal failure) 11 (18%) pts had SAEs	1 treatment-related death (sepsis) and 4 non-treatment related deaths (pneumonitis, liver graft failure, cariogenic shock, sepsis)
After liver transplantation									
Coilly *et al*[37]	37	Cohort study	BOC/PEG-IFN/RBV (*n* = 18) TVR/PEG-IFN/RBV (*n* = 19)	12 wk	1	CyA (*n* = 22) TAC (*n* = 15)	Complete virological response: BOC 89% and TVR 58% (*P* = 0.06) SVR: BOC 71% and TVR 20%	Therapy discontinuation in 16 (lack of efficacy 11, AEs 5). Infections in 27%, 3 (8%) fatal Most common AE anemia (92%), treated with EPO and/or a RBV dose reduction; 35% required red blood cell transfusions	CyA and TAC dose reductions required
Werner *et al*[38]	9	Pilot study	TVR/PEG-IFN/RBV	12 wk	1	CyA (*n* = 4) TAC (*n* = 4) SIR (*n* = 1)	4/9 pts HCV RNA negative at wk 4	Hematological AEs requiring RBV dose reductions, EPO or transfusions in 2/3rds of pts	Dose reductions in all patients (CyA, 2.5-fold; SIR, 7-fold; and TAC, 22-fold)
Werner *et al*[70]	9	Long-term follow-up	TVR/PEG-IFN/RBV	48 wk (= 24 wk follow-up after EOT)	1	CyA (*n* = 4) TAC (*n* = 4) SIR (*n* = 1)	SVR at wk 24 after EOT in 5/9	2 pts discontinued due to AEs	5/9 completed 48 wk' therapy
Rogers *et al*[44]	2	Case report	TVR/PEG-IFN/RBV	NS	NS	TAC	HCV RNA undetectable at 10 wk in 1 pt (NS in pt 2)	NS	TAC dose adjustment required
Burton and Everson[39]	12	Retrospective	TVR/PEG-IFN/RBV	12 wk	NS	CyA	Wk 4: 11/12 pts had HCV RNA < 43 IU/mL	Anemia; 5 pts required transfusion	2 pts developed TVR resistance
Pungpapong *et al*[42]	7	OL study	TVR/PEG-IFN/RBV	12 wk	1	CyA	83% HCV RNA < 1000 IU/mL at wk 4	TVR discontinued due to severe anemia in 12 pt; 5 pts required EPO and 2 filgrastim	Graft rejection in 1 pt CyA dose adjustment required
de Oliveira Pereira *et al*[40]	6	OL study	TVR/PEG-IFN/RBV	5 wk	1	CyA	2 pts achieved SVR at 5 wk (one was persistent at 12 wk)	Tolerated in 5/6 pts; 1 pt discontinued due to rash and headache	NR
Reddy and Everson[46]	1	Case report	BOC/PEG-IFN/RBV	32 wk	1	TAC	HCV RNA undetectable at wk 12 of TT	AEs: fatigue, anemia, and syncope, requiring hospital admission. Anemia managed with RBV dose reduction, EPO and transfusion	TAC dose reduction
Sam *et al*[47]	3	Case report	BOC (800 mg q8h)/PEG-IFN/RBV	19 d	NS	CyA	NS	NS	Minor increased CyA concentrations, requiring dose adjustments

Schilsky *et al*[48]	3	Case report	BOC (800 mg q8h)/PEG-IFN/RBV	19 d	NS	CyA	1 pt achieved undetectable HCV-RNA and one achieved > 2log decrease by day 19; significant improvement in liver tests Histological improvement only in pt 3	Fatigue (did not require discontinuation)	-
Forns *et al*[54]	87	NS	SOF (400 mg)/RBV ± PEG-INF	48 wk	1 (*n* = 72) 2 (*n* = 2) 3 (*n* = 6) 4 (*n* = 3) Mixed (*n* = 4)	NS	SVR at 12 wk: SOF/RBV 54% and SOF/RBV/PEG-INF 44%	SAEs reported by 33% of pts (none attributable to study drug)	13 pts (17%) dead, all due to progression of liver disease or associated complications
Samuel *et al*[1]	40	OL study	SOF (400 mg)/RBV	24 wk	1 (*n* = 22) 2 (*n* = 11) 3 (*n* = 6) 4 (*n* = 1)	NS	HCV RNA undetectable at wk 4 in all pts 27 pts out of 35 achieved SVR at 4 wk	2 pts discontinued due to pneumonia and HCV progression AEs: fatigue, headache, arthralgia, diarrhea	

AE: Adverse event; BOC: Boceprevir; CHC: Chronic hepatitis C; CyA: Cyclosporine; EOT: End of therapy; EPO: Erythropoietin; HCV: Hepatitis C virus; LT: Liver transplantation; MMF: Mycophenolate mofetil; NA: Not applicable; NS: Not stated; pbo: Placebo; PEG-IFN: Pegylated interferon; PRED: Prednisone; pts: Patients; pTVR12: Post-transplant virologic response 12 wk after transplant; RBV: Ribavirin; SAEs: Serious adverse events; SIR: Sirolimus; SOF: Sofosbuvir; SVR: Sustained virological response; TAC: Tacrolimus; TT: Triple therapy; TVR: Telaprevir.

with immunosuppressants cyclosporine and tacrolimus were easily managed[45].

Early single-center data have shown efficacy of BOC in severe recurrent HCV as part of a triple therapy regimen with PEG-IFN/RBV in three post-LT patients receiving CyA (two with fibrosing cholestatic hepatitis and one with stage 2-3 fibrosis)[46-48].

TOLERABILITY OF IFN AND PIS IN THE PRE-AND POST-LT SETTING

IFNs are associated with poor tolerability in many patients in the pre- and post-LT settings and so their use requires very careful monitoring[10]. Dose reductions and treatment discontinuation are required in > 50% of patients[1].

In patients with cirrhosis (particularly in those with decompensated cirrhosis), IFN/RBV becomes an even less well tolerated treatment, being contraindicated in those with Child-Pugh C cirrhosis due to a high risk of life threatening conditions[1,9,10,49,50]. The occurrence of hematological adverse events with IFN/RBV regimens increases with severity of liver disease due to portal hypertension; close monitoring and dose modifications are required to minimize cytopenic effects[1]. Growth factors and transfusion are often required to allow effective IFN doses to be continued[1,6,51].

In the post-LT setting, TVR and BOC exhibit hematologic toxicity, renal dysfunction and an increased risk of severe infections[1]. However, most of the data to date is in triple therapy regimens with PEG-IFN and RBV and thus it is possible that the origin of most AEs can be attributed to IFN/RBV; nonetheless, the addition of PI most definitely contributes to the worsening of the events both in term of frequency and severity.

NOVEL THERAPIES

Several DAA-based combination therapies are being investigated for the treatment of HCV infection in the LT setting[1]. The new DAAs act on specific viral components[52]; while the accepted definition of clinical response with current antiviral treatment is SVR achievement at 24 wk, for newer DAA agents this has been reduced to 12 wk[53].

Sofosbuvir, a recently-approved nucleotide analogue inhibitor of the HCV NS5B polymerase enzyme with pan-genotypic activity, has been studied in HCV genotypes 1-6 and its efficacy has been established in a wide range of patients[54,55]. A Phase 2 study of sofosbuvir/RBV was performed in pre-transplant patients with HCC to evaluate prevention of recurrent HCV following LT, assessed by post-LT virological response at week 12[56]. Of those patients with undetectable HCV-RNA at the time of transplantation following treatment, 70% (30/43) had a post-transplant virological response (ptSVR12). The strongest predictors of post-LT viral response (*i.e.*, prevention of recurrence) was the number of days with undetectable HCV RNA prior to LT. Treatment with sofosbuvir/RBV was well-tolerated, with only two patients (3%) having an AE that led to study discontinuation, and none of the AEs leading to discontinuation were considered related to sofosbuvir by the investigators[56]. Although the safety and efficacy of sofosbuvir is not fully established in post-LT patients, preliminary results have shown an SVR4 in 77% of patients who experience recurrent HCV post-LT and treated with sofosbuvir/RBV for 24 wk[57]. Moreover,

dual-therapy regimen with sofosbuvir and the NS5A-inhibitor daclatasvir has been described in a post-LT patient with severe recurrent cholestatic hepatitis C leading to rapid and sustained suppression of HCV replication[58].

Sofosbuvir was provided in an approved compassionate use protocol to treat patients with severe recurrent HCV infection following LT, including patients with fibrosing cholestatic hepatitis and life expectancy < 1 year. The regimen included sofosbuvir 400 mg/d for up to 48 wk, with appropriate doses of RBV ± PEG-IFN at the physician's discretion[54]. SVR12 rates were 54% with sofosbuvir + RBV and 44% for those treated with sofosbuvir + RBV + PEG-IFN, and treatment resulted in notable clinical improvement and/or disease stabilization[54].

The use of sofosbuvir 400 mg/d + daclatasvir 60 mg/d was also evaluated in a compassionate use program in 12 patients with HCV recurrence after LT and was shown to achieve SVR4 in 82% and SVR12 in 100% with improvement in liver-related assessments in the majority of patients at week 12[59]. Combination daclatasvir/simeprevir/RBV is being investigated in post-LT patients with HCV G1b infection (ClinicalTrials.gov NCT01938625). Other agents in development for use post-LT include silibinin-an HCV RNA polymerase inhibitor - in development for treatment/prevention of HCV (with PEG-IFN ± RBV) post-LT[60-62].

A DAA-based IFN-free regimen is being investigated in an ongoing open-label phase 2 study; 24 wk' treatment with the combination ABT-450/ritonavir/ombitasvir + HCV non-nucleoside inhibitor dasabuvir ± RBV is being investigated in a study of 34 adult non-cirrhotic LT recipients with recurrent HCV G1 infection; the interim data are promising, showing that all 34 patients achieved an RVR and of the 13 patients who have completed the full treatment course, the SVR4 rate was 92% (12/13) with no episodes of acute rejection[63].

The first case of a patient with fibrosing cholestatic hepatitis C after LT treated with sofosbuvir and simeprevir was presented at EASL 2014[64]. A 59-year-old woman switched from PEG-IFN/TVR/RBV due to severe side effects to sofosbuvir and simeprevir + RBV achieved undetectable HCV after 8 wk' treatment with the added benefit of normalized liver parameters and no serious side effects, indicating that this regimen may be an option for difficult to treat patients with severe CHC after LT[64].

Due to an optimal tolerability and safety profile and an absence of relevant drug-to-drug interactions, IFN-sparing DAAs (such as protease inhibitors, polymerase or other non-structural proteins inhibitors) represent a new era in HCV-associated liver disease. Indeed SVR rates of 90%-95% have been observed in pre- and post-LT, thus providing extraordinary tools in the management of both pre- and post-transplant HCV infection. The next steps for this new form of treatment is to establish which strategy is most cost-effective in tackling hepatitis C: preventing graft infection by treating patients before LT or treating hepatitis C recurrence after LT.

PHARMACOECONOMIC CONSIDERATIONS

Economic analyses show that average annual costs for compensated or decompensated cirrhosis are €20000 and €60000, respectively[65]. LT-associated costs are even higher (about €150000 annually)[66]. Prompt and targeted HCV treatment could decrease transplant risk or post-LT relapse rate, and limit CHC treatment costs. Since hepatitis is progressive, the costs incurred for treatment of associated clinical consequences will increase depending on the worsening pathology[67]. A US retrospective analysis in > 50000 HCV patients, compensated cirrhosis and ESLD led to 32% and 247% increases in treatment costs/month, respectively, *vs* no cirrhosis, independent of age and comorbidity[18].

Indirect costs due to lost work productivity also have to be considered. According to European survey results, HCV patients are characterized by greater lost work productivity than the healthy population ($P < 0.05$)[24]. Similar results from an observational, multicenter cost-of-illness study in Italy[68] showed direct correlation between liver disease progression and increase in the monthly average costs/patient: € 240 for CHC treatment, €500 for cirrhosis treatment, € 1230 for HCC, and €2680 for LT[68]. Average lost work productivity was 8 d/year/patient, with high variability depending on the health status of the patient (5-21 d/year/patient for non-cirrhotic CHC, HCC, and LT)[68].

It is clear that discussion of treatment costs for management of CHC patients waiting for LT includes costs associated with antiviral therapy, hospitalization, additional therapies to treat side effects, and monitoring. Pre-LT, using antiviral therapy required a constant monitoring of patient condition and continuous dosage corrections. The administration of growth factors, like erythropoietin and filgrastim, is often needed to control hematological side effects. In addition, higher healthcare costs due to low efficacy of dual therapy should be considered. In fact, the low SVR rate achieved with the dual therapy could cause subsequent relapse in transplanted patients with a resulting worsening of clinical condition (fibrosis, cirrhosis, second transplantation, *etc.*) and further increase in health care costs.

In a recent phase Ⅱ trial of sofosbuvir/ribavirin antiviral treatment in pre-LT patients with compensated cirrhosis (all genotypes, HCV RNA < 25 UI/mL pre-LT), there was good tolerability, and HCV recurrence was prevented in 70% of patients who had HCV RNA < lower limit of quantification (LLOQ) at transplant[56].

These clinical results, which led to the European approval of sofosbuvir also for pre-LT HCV treatment, were used for a cost-effectiveness model applied to

the Italian healthcare system which demonstrated the effectiveness of sofosbuvir/RBV in these patients[69]. The model compared sofosbuvir/RBV as prophylactic therapy before LT or conventional post-LT dual antiviral therapy. The results showed sofosbuvir as a cost-effective strategy with a cost per QALY (quality adjusted life-year) of €31895 compared to conventional post-LT dual antiviral therapy.

Cost estimation for post-transplant antiviral therapy is similar and includes antiviral therapy, side effect management, drug interactions and monitoring. Low therapy effectiveness leads to worsening of the clinical condition, and increased health care costs.

CONCLUSION

IFN-based dual or triple-drug antiviral strategies for HCV are useful before transplant to reduce HCV viral load in order to prevent or reduce the risk of post-LT recurrence and complications. However, they can only be used in about half of HCV-infected patients who are candidates for LT. After LT, use of currently approved agents is limited due to tolerability issues, contraindications and other issues.

The future availability of new IFN-free antiviral therapy could change the present clinical and economic scenario considerably. The better efficacy and tolerability of novel regimens could increase SVR rates and decrease side effects, drug interactions and prevent worsening of CHC, decreasing costs associated with HCV treatment in transplanted patients and worsening of patient health. This conclusion needs to be confirmed by more in-depth economic studies.

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REFERENCES

1 **European Association for Study of Liver**. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2014; **60**: 392-420 [PMID: 24331294 DOI: 10.1016/j.jhep.2013.11.003]

2 **Kim WR**, Stock PG, Smith JM, Heimbach JK, Skeans MA, Edwards EB, Harper AM, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2011 Annual Data Report: liver. *Am J Transplant* 2013; **13** Suppl 1: 73-102 [PMID: 23237697 DOI: 10.1111/ajt.12021]

3 **Italian Association for the Study of the Liver**, (Italian Society of Infectious, Tropical Diseases), Italian Society for the Study of Sexually Transmitted Diseases. Practice guidelines for the treatment of hepatitis C: recommendations from an AISF/SIMIT/SIMAST Expert Opinion Meeting. *Dig Liver Dis* 2010; **42**: 81-91 [PMID: 19748329 DOI: 10.1016/j.dld.2009.08.001]

4 **Gane E**. The natural history and outcome of liver transplantation in hepatitis C virus-infected recipients. *Liver Transpl* 2003; **9**: S28-S34 [PMID: 14586892 DOI: 10.1053/jlts.2003.50248]

5 **Ciria R**, Pleguezuelo M, Khorsandi SE, Davila D, Suddle A, Vilca-Melendez H, Rufian S, de la Mata M, Briceño J, Cillero PL, Heaton N. Strategies to reduce hepatitis C virus recurrence after liver transplantation. *World J Hepatol* 2013; **5**: 237-250 [PMID: 23717735 DOI: 10.4254/wjh.v5.i5.237]

6 **Davis GL**. New approaches and therapeutic modalities for the prevention and treatment of recurrent HCV after liver transplantation. *Liver Transpl* 2003; **9**: S114-S119 [PMID: 14586906 DOI: 10.1053/jlts.2003.50246]

7 **Agarwal K**, Barnabas A. Treatment of chronic hepatitis C virus infection after liver transplantation. *Dig Liver Dis* 2013; **45** Suppl 5: S349-S354 [PMID: 24091115 DOI: 10.1016/j.dld.2013.07.014]

8 **Firpi RJ**, Clark V, Soldevila-Pico C, Morelli G, Cabrera R, Levy C, Machicao VI, Chaoru C, Nelson DR. The natural history of hepatitis C cirrhosis after liver transplantation. *Liver Transpl* 2009; **15**: 1063-1071 [PMID: 19718647 DOI: 10.1002/lt.21784]

9 **Forns X**, García-Retortillo M, Serrano T, Feliu A, Suarez F, de la Mata M, García-Valdecasas JC, Navasa M, Rimola A, Rodés J. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. *J Hepatol* 2003; **39**: 389-396 [PMID: 12927925]

10 **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]

11 **Colombo M**, Fernández I, Abdurakhmanov D, Ferreira PA, Strasser SI, Urbanek P, Moreno C, Streinu-Cercel A, Verheyen A, Iraqi W, DeMasi R, Hill A, Läuffer JM, Lonjon-Domanec I, Wedemeyer H. Safety and on-treatment efficacy of telaprevir: the early access programme for patients with advanced hepatitis C. *Gut* 2014; **63**: 1150-1158 [PMID: 24201995 DOI: 10.1136/gutjnl-2013-305667]

12 **Hézode C**, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, de Ledinghen V, Poynard T, Samuel D, Bourlière M, Zarski JP, Raabe JJ, Alric L, Marcellin P, Riachi G, Bernard PH, Loustaud-Ratti V, Métivier S, Tran A, Serfaty L, Abergel A, Causse X, Di Martino V, Guyader D, Lucidarme D, Grando-Lemaire V, Hillon P, Feray C, Dao T, Cacoub P, Rosa I, Attali P, Petrov-Sanchez V, Barthe Y, Pawlotsky JM, Pol S, Carrat F, Bronowicki JP. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *J Hepatol* 2013; **59**: 434-441 [PMID: 23669289 DOI: 10.1016/j.jhep.2013.04.035]

13 **Joshi D**, Carey I, Agarwal K. Review article: the treatment of genotype 1 chronic hepatitis C virus infection in liver transplant candidates and recipients. *Aliment Pharmacol Ther* 2013; **37**: 659-671 [PMID: 23432320 DOI: 10.1111/apt.12260]

14 **Londoño MC**, Crespo G, Forns X. Pretransplant and posttransplant treatment of hepatitis C virus infection with protease inhibitors. *Curr Opin Organ Transplant* 2013; **18**: 271-278 [PMID: 23665543 DOI: 10.1097/MOT.0b013e3283614aca]

15 **Bruno S**, Stroffolini T, Colombo M, Bollani S, Benvegnù L, Mazzella G, Ascione A, Santantonio T, Piccinino F, Andreone P, Mangia A, Gaeta GB, Persico M, Fagiuoli S, Almasio PL. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 2007; **45**: 579-587 [PMID: 17326216 DOI: 10.1002/hep.21492]

16 **Singal AG**, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clin Gastroenterol Hepatol* 2010; **8**: 280-828, 288.e1 [PMID: 19948249 DOI: 10.1016/j.cgh.2009.11.018]

17 **van der Meer AJ**, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308**: 2584-2593 [PMID: 23268517

DOI: 10.1001/jama.2012.144878]
18 **Gordon SC**, Pockros PJ, Terrault NA, Hoop RS, Buikema A, Nerenz D, Hamzeh FM. Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection. *Hepatology* 2012; **56**: 1651-1660 [PMID: 22610658 DOI: 10.1002/hep.25842]
19 **Everson GT**, Hoefs JC, Seeff LB, Bonkovsky HL, Naishadham D, Shiffman ML, Kahn JA, Lok AS, Di Bisceglie AM, Lee WM, Dienstag JL, Ghany MG, Morishima C. Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: Lessons from the HALT-C trial. *Hepatology* 2006; **44**: 1675-1684 [PMID: 17133499 DOI: 10.1002/hep.21440]
20 **Sánchez-Tapias JM**, Diago M, Escartín P, Enríquez J, Romero-Gómez M, Bárcena R, Crespo J, Andrade R, Martínez-Bauer E, Pérez R, Testillano M, Planas R, Solá R, García-Bengoechea M, Garcia-Samaniego J, Muñoz-Sánchez M, Moreno-Otero R. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006; **131**: 451-460 [PMID: 16890599 DOI: 10.1053/j.gastro.2006.05.016]
21 **Shiffman ML**, Di Bisceglie AM, Lindsay KL, Morishima C, Wright EC, Everson GT, Lok AS, Morgan TR, Bonkovsky HL, Lee WM, Dienstag JL, Ghany MG, Goodman ZD, Everhart JE. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology* 2004; **126**: 1015-1023; discussion 947 [PMID: 15057741]
22 **Berenguer M**, Charco R, Manuel Pascasio J, Ignacio Herrero J. Spanish society of liver transplantation (SETH) consensus recommendations on hepatitis C virus and liver transplantation. *Liver Int* 2012; **32**: 712-731 [PMID: 22221843 DOI: 10.1111/j.1478-3231.2011.02731.x]
23 **Guido M**, Fagiuoli S, Tessari G, Burra P, Leandro G, Boccagni P, Cillo U, Naccarato R, Rugge M. Histology predicts cirrhotic evolution of post transplant hepatitis C. *Gut* 2002; **50**: 697-700 [PMID: 11950819]
24 **Vietri J**, Prajapati G, El Khoury AC. The burden of hepatitis C in Europe from the patients' perspective: a survey in 5 countries. *BMC Gastroenterol* 2013; **13**: 16 [PMID: 23324473 DOI: 10.1186/1471-230X-13-16]
25 **Everson GT**, Trotter J, Forman L, Kugelmas M, Halprin A, Fey B, Ray C. Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. *Hepatology* 2005; **42**: 255-262 [PMID: 16025497 DOI: 10.1002/hep.20793]
26 **Everson GT**, Terrault NA, Lok AS, Rodrigo del R, Brown RS, Saab S, Shiffman ML, Al-Osaimi AM, Kulik LM, Gillespie BW, Everhart JE. A randomized controlled trial of pretransplant antiviral therapy to prevent recurrence of hepatitis C after liver transplantation. *Hepatology* 2013; **57**: 1752-1762 [PMID: 22821361 DOI: 10.1002/hep.25976]
27 **Braithwaite A**, Aguilera V, Vinaixa C, Garcia M, Benlloch S, Rubin A, Prieto M, Berenguer M. Triple therapy for HCV cirrhosis in liver transplant candidates. High rate of prevention of HCV recurrence after liver transplantation (LT) in well selected patients [P1207]. *J Hepatol* 2014; **60** (Suppl): S361-S522
28 **Castells L**, Vargas V, Allende H, Bilbao I, Luis Lázaro J, Margarit C, Esteban R, Guardia J. Combined treatment with pegylated interferon (alpha-2b) and ribavirin in the acute phase of hepatitis C virus recurrence after liver transplantation. *J Hepatol* 2005; **43**: 53-59 [PMID: 15876467 DOI: 10.1016/j.jhep.2005.02.015]
29 **Gurakar A**, Fagiuoli S, Hassanein T, Kingery L, Wright HI, Ersoz S, Caraceni P, Gavaler JS, Van Thiel DH. Prophylactic alpha-interferon therapy following liver transplantation: does it prevent allograft infection? *Eur J Gastroenterol Hepatol* 1994; **6**: 429-432
30 **Ponziani FR**, Gasbarrini A, Pompili M, Burra P, Fagiuoli S. Management of hepatitis C virus infection recurrence after liver transplantation: an overview. *Transplant Proc* 2011; **43**: 291-295 [PMID: 21335208 DOI: 10.1016/j.transproceed.2010.09.102]
31 **Gallegos-Orozco JF**, Yosephy A, Noble B, Aqel BA, Byrne TJ, Carey EJ, Douglas DD, Mulligan D, Moss A, de Petris G, Williams JW, Rakela J, Vargas HE. Natural history of post-liver transplantation hepatitis C: A review of factors that may influence its course. *Liver Transpl* 2009; **15**: 1872-1881 [PMID: 19938138 DOI: 10.1002/lt.21954]
32 **Gane EJ**. The natural history of recurrent hepatitis C and what influences this. *Liver Transpl* 2008; **14** Suppl 2: S36-S44 [PMID: 18825724 DOI: 10.1002/lt.21646]
33 **Hashemi N**, Araya V, Tufail K, Thummalakunta L, Feyssa E, Azhar A, Niazi M, Ortiz J. An extended treatment protocol with pegylated interferon and ribavirin for hepatitis C recurrence after liver transplantation. *World J Hepatol* 2011; **3**: 198-204 [PMID: 21866251 DOI: 10.4254/wjh.v3.i7.198]
34 **Perrakis A**, Yedibela S, Schuhmann S, Croner R, Schellerer V, Demir R, Hohenberger W, Müller V. The effect and safety of the treatment of recurrent hepatitis C infection after orthotopic liver transplantation with pegylated interferon α2b and ribavirin. *Transplant Proc* 2011; **43**: 3824-3828 [PMID: 22172854 DOI: 10.1016/j.transproceed.2011.08.103]
35 **Ikegami T**, Shirabe K, Yoshizumi T, Furusyo N, Kotoh K, Kato M, Shimoda S, Soejima Y, Motomura T, Fukuhara T, Maehara Y. Impact of conversion from pegylated interferon-α2b to interferon-α2a for treating recurrent hepatitis C after liver transplantation. *Transplantation* 2013; **95**: e38-e42 [PMID: 23507656 DOI: 10.1097/TP.0b013e318283a82e]
36 **Takeishi K**, Shirabe K, Toshima T, Ikegami T, Morita K, Fukuhara T, Motomura T, Mano Y, Uchiyama H, Soejima Y, Taketomi A, Maehara Y. De novo autoimmune hepatitis subsequent to switching from type 2b to type 2a alpha-pegylated interferon treatment for recurrent hepatitis C after liver transplantation: report of a case. *Surg Today* 2011; **41**: 1016-1019 [PMID: 21748625 DOI: 10.1007/s00595-010-4392-z]
37 **Coilly A**, Roche B, Dumortier J, Leroy V, Botta-Fridlund D, Radenne S, Pageaux GP, Si-Ahmed SN, Guillaud O, Antonini TM, Haïm-Boukobza S, Roque-Afonso AM, Samuel D, Duclos-Vallée JC. Safety and efficacy of protease inhibitors to treat hepatitis C after liver transplantation: a multicenter experience. *J Hepatol* 2014; **60**: 78-86 [PMID: 23994384 DOI: 10.1016/j.jhep.2013.08.018]
38 **Werner CR**, Egetemeyr DP, Lauer UM, Nadalin S, Königsrainer A, Malek NP, Berg CP. Telaprevir-based triple therapy in liver transplant patients with hepatitis C virus: a 12-week pilot study providing safety and efficacy data. *Liver Transpl* 2012; **18**: 1464-1470 [PMID: 22941516 DOI: 10.1002/lt.23542]
39 **Burton J**, Everson GT. Initial experience with telaprevir for treating hepatitis C virus in liver recipients: virologic response, safety, and tolerability [abstract #LB01]. American Transplant Congress: ATC, 2012
40 **de Oliveira Pereira AP**, Shin HJ, Safdar A, Tobias H, Gelb B, Morgan G, Diflo T, Winnick A, Teperman L. Post liver transplant therapy with telaprevir for recurrent hepatitis C [abstract #1369]. American Transplant Congress: ATC, 2012
41 **Forns X**, Samuel D, Mutimer D, Fagiouli S, Navasa M, Agarwal K, Berenguer M, Colombo M, Herzer K, Nevens F, Van Solingen-Ristea R, Luo D, Dierynck I, Witek J. Interim SVR12 results from the telaprevir phase 3b replace study in treatment-naïve stable liver transplant patients with genotype 1 HCV infection [P1185]. *J Hepatol* 2014; **60** (Suppl): S361-S522
42 **Pungpapong S**, Murphy J, Henry T, Satyanarayana R, Rosser B, Yataco M, Harnois D, Patel T, Keaveny A. Initial experience utilizing telaprevir with peginterferon and ribavirin for treatment of hepatitis C genotype 1 after liver transplantation [abstract #1367]. American Transplant Congress: ATC, 2012
43 **Werner CR**, Egetemeyr DP, Nadalin S, Königsrainer A, Malek NP, Lauer UM, Berg CP. Telaprevir-triple therapy of recurrent HCV genotype 1 (G1) infection after liver transplantation (LTx): SVR 24 results [P902]. *J Hepatol* 2014; **60** (Suppl): S361-S522
44 **Rogers CC**, Stevens DR, Kim M, Ghaziani T, Malik R, Curry MP. Telaprevir can be used safely with concomitant tacrolimus in the post-transplant setting [abstract #1372]. American Transplant Congress: ATC, 2012
45 **Antonini TM**, Furlan V, Teicher E, Haim-Boukobza S, Sebagh M, Coilly A, Bonhomme-Faivre L, Roque-Afonso A-M, Vittecoq D,

Samuel D, Taburet A-M, Duclos-Vallee J-C. Anti-hepatitis C (HCV) triple therapy with protease inhibitors in HIV/HCV co-infected patients after liver transplantation [P1237]. *J Hepatol* 2014; **60** (Suppl): S361-S522

46 **Reddy KR**, Everson GT. Treatment of chronic hepatitis C with protease inhibitor-based therapy after liver transplantation. *Hepatology* 2013; **58**: 1181-1184 [PMID: 23908010 DOI: 10.1002/hep.26612]

47 **Sam T**, Tichy E, Emre S, Schilsky M. Pharmacokinetic effects of boceprevir co-administration on cyclosporine exposure in liver transplant recipients [abstract #1370]. American Transplant Congress: ATC, 2012

48 **Schilsky M**, Sam T, Tichy E, Caldwell C, Jakab S, Emre S. Boceprevir, peginterferon and ribavirin (PEGIFN/RIB) as triple antiviral therapy for severe recurrent hepatitis C post liver transplant: an early single center experience [abstract #1377]. American Transplant Congress: ATC, 2012

49 **Alves de Mattos A**, Zambam de Mattos A. Treatment of HCV infection in patients with cirrhosis. *Ann Hepatol* 2010; **9** Suppl: 80-83 [PMID: 20714001]

50 **Samuel D**, Bizollon T, Feray C, Roche B, Ahmed SN, Lemonnier C, Cohard M, Reynes M, Chevallier M, Ducerf C, Baulieux J, Geffner M, Albrecht JK, Bismuth H, Trepo C. Interferon-alpha 2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: a randomized study. *Gastroenterology* 2003; **124**: 642-650 [PMID: 12612903 DOI: 10.1053/gast.2003.50095]

51 **Fredrick RT**, Hassanein TI. Role of growth factors in the treatment of patients with HIV/HCV coinfection and patients with recurrent hepatitis C following liver transplantation. *J Clin Gastroenterol* 2005; **39**: S14-S22 [PMID: 15597023]

52 **Sarrazin C**, Hézode C, Zeuzem S, Pawlotsky JM. Antiviral strategies in hepatitis C virus infection. *J Hepatol* 2012; **56** Suppl 1: S88-100 [PMID: 22300469 DOI: 10.1016/S0168-8278(12)60010-5]

53 **Kim do Y**, Ahn SH, Han KH. Emerging therapies for hepatitis C. *Gut Liver* 2014; **8**: 471-479 [PMID: 25228970 DOI: 10.5009/gnl14083]

54 **Forns X**, Prieto M, Charlton M, McHutchison JG, Symonds WT, Denning J, Brandt-Sarif T, Chang P, Kivett V, Fontana RJ, Baumert TF, Coilly A, Castells L, Habersetzer F. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C including fibrosing cholestatic hepatitis following liver transplantation [abstract 062]. *J Hepatol* 2014; **60** (Suppl): S23-S44

55 **Gilead Sciences I**. FDA Advisory Committee Supports Approval of Gilead's Sofosbuvir for Chronic Hepatitis C Infection, 2013

56 **Curry MP**, Forns X, Chung RT, Terrault NA, Brown RS, Jr., Fenkel JM, Gordon F, O'Leary JG, Kuo A, Schiano T, Everson GT, Schiff ER, Befeler A, McHutchison JG, Symonds WT, Denning J, McNair L, Arterburn S, Moonka D, Gane E, Afdhal N. Pretransplant sofosbuvir and ribavirin to prevent recurrence of HCV infection after liver transplantation [AASLD abstract 213]. *Hepatology* 2013; **58**: 314A

57 **Samuel D**, Charlton M, Gane E, Brown J, R. , Curry M, Kwo P, Fontana R, Gilroy R, Teperman L, Muir AJ, McHutchison JG, Symonds WT, Denning J, McNair L, Arterburn S, Terrault N, Forns X, Manns M. Sofosbuvir and ribavirin for the treatment of recurrent hepatitis C infection after liver transplantation: results of a prospective multicenter study [P1232]. *J Hepatol* 2014; **60** (Suppl): S361-S522

58 **Fontana RJ**, Hughes EA, Bifano M, Appelman H, Dimitrova D, Hindes R, Symonds WT. Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C. *Am J Transplant* 2013; **13**: 1601-1605 [PMID: 23593993 DOI: 10.1111/ajt.12209]

59 **Pellicelli AM**, Lionetti R, Montalbano M, Durand C, Ferenci P, D'Offizi G, Knop V, Telese A, Lenci I, Andreoli A, Zeuzem S, Angelico M. Sofosbuvir and daclatasvir for recurrent hepatitis C after liver transplantation: potent antiviral activity but lack of clinical benefit if treatment is given too late [P1312]. *J Hepatol* 2014; **60** (Suppl): S523-S537

60 **Bárcena R**, Moreno A, Rodríguez-Gandía MA, Albillos A, Arocena C, Blesa C, García-Hoz F, Graus J, Nuño J, López-Hervás P, Gajate L, Martínez A, Bermejo T, Mateos ML, Del Campo S. Safety and anti-HCV effect of prolonged intravenous silibinin in HCV genotype 1 subjects in the immediate liver transplant period. *J Hepatol* 2013; **58**: 421-426 [PMID: 23073223 DOI: 10.1016/j.jhep.2012.10.009]

61 **Mariño Z**, Crespo G, D'Amato M, Brambilla N, Giacovelli G, Rovati L, Costa J, Navasa M, Forns X. Intravenous silibinin monotherapy shows significant antiviral activity in HCV-infected patients in the peri-transplantation period. *J Hepatol* 2013; **58**: 415-420 [PMID: 23063567 DOI: 10.1016/j.jhep.2012.09.034]

62 **Neumann UP**, Biermer M, Eurich D, Neuhaus P, Berg T. Successful prevention of hepatitis C virus (HCV) liver graft reinfection by silibinin mono-therapy. *J Hepatol* 2010; **52**: 951-952 [PMID: 20413176 DOI: 10.1016/j.jhep.2010.02.002]

63 **Kwo P**, Mantry P, Coakley E, Te H, Vargas H, Brown Jr. R, Gordon F, Levitsky J, Terrault N, Burton Jr. J, Xie W, Setze C, Badri P, Vilchez RA, Forns X. Results of the phase 2 study M12-999: interferon-free regimen of ABT-450/R/ABT-267 ABT-333 ribavirin in liver transplant recipients with recurrent HCV genotype 1 infection [P0114]. *J Hepatol* 2014; **60** (Suppl): S45-S66

64 **Lang M**, Polywka S, Kluwe J, Fischer L, Jordan S, Lütgehetmann M, Nashan B, Lohse AW, Sterneck M. First case report of a patient with fibrosing cholestatic hepatitis C after liver transplantation treated with sofosbuvir and simeprevir [P875]. *J Hepatol* 2014; **60** (Suppl): S361-S522

65 **Logge C**, Vettorazzi E, Fischer L, Nashan B, Sterneck M. Cost-effectiveness analysis of antiviral treatment in liver transplant recipients with HCV infection. *Transpl Int* 2013; **26**: 527-534 [PMID: 23517333 DOI: 10.1111/tri.12085]

66 **Libro Bianco AISF**. Proposta per un piano nazionale per il controllo delle malattie epatiche. Definizione ambiti e possibili interventi: Fondazione Italiana per la Ricerca in Epatologia, 2011

67 **Carosi G**, Caporaso N, Gardini I, Mazzotta F, Prati D, Rizzetto M, Rossi A, Salvagnini M, Taliani G. Epatiti Summit. Un'emergenza sommersa: opinioni e strategie a confronto, 2010

68 **Ciampichini R**, Scalone L, Fagiuoli S, Fusco F, Gaeta L, Del prete A, Gardini I, Mantovani L. Societal burden in hepatitis C patients: the COME study results. *Value Health* 2012; **15**: A138

69 **Vitale A**, Spolverato G, Burra P, De Feo TM, Belli L, Donato F, Svegliati Baroni G, Marianelli T, Picciotto A, Toniutto P, Bhoori S, Passigato N, Lucà MG, Cillo U, Fagiuoli S, on behalf of the Liver Transplantation NITp working group. Potential net health benefit of pre-transplant Sofosbuvir to prevent recurrence of HCV infection after liver transplantation: A multicenter, cohort model study. *Dig Liver Dis* 2014; **46** Suppl 4: e.132-e.133 [DOI: 10.1016/j.dld.2014.08.012]

70 **Werner CR**, Egetemeyr DP, Lauer UM, Nadalin S, Königsrainer A, Malek NP, Berg CP. Feasibility of telaprevir-based triple therapy in liver transplant patients with hepatitis C virus: SVR 24 results. *PLoS One* 2013; **8**: e80528 [PMID: 24265827 DOI: 10.1371/journal.pone.0080528]

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