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# Management of hepatitis C infection before and after liver transplantation

Fagiuoli S *et al.* HCV treatment pre- and post-liver transplant

Stefano Fagiuoli, Roberto Ravasio, Maria Grazia Lucà, Anna Baldan, Silvia Pecere, Alessandro Vitale, Luisa Pasulo

**Stefano Fagiuoli, Maria Grazia Lucà, Anna Baldan, Silvia Pecere, Luisa Pasulo,** Gastroenterology and Transplant Hepatology, Papa Giovanni XXIII Hospital, 24127 Bergamo, Italy

**Roberto Ravasio,** PHarmES Milano, 20133 Milano, Italy

**Alessandro Vitale,** Liver Transplantation and Hepatobiliary Surgical Unit, Padua University Hospital, 35122 Padua, Italy

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**Correspondence to:** **Dr. Stefano Fagiuoli, USC,** Gastroenterology and Transplant Hepatology, Papa Giovanni XXIII Hospital, Piazza OMS, 1, 24127 Bergamo, Italy. sfagiuoli@hpg23.it

**Telephone**: +35-2-673459

**Fax:** +35-2-674964

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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 versus 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 transplantation; Interferon-free treatment; Decompensated cirrhosis; Chronic hepatitis C

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**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](#_ENREF_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](#_ENREF_2)]. In Italy, HCV-related ESLD accounts for 30%-40% of LTs[[3](#_ENREF_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](#_ENREF_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](#_ENREF_1),[5](#_ENREF_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](#_ENREF_1),[5](#_ENREF_5),[6](#_ENREF_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](#_ENREF_7),[8](#_ENREF_8)].

At present, interferon (IFN)-based regimens are contraindicated in many patients with cirrhosis and in all with decompensated disease[[9](#_ENREF_9)]. IFN-based HCV treatment after LT is poorly tolerated due to severe side effects (particularly anemia and infections) resulting in poor outcomes[[6](#_ENREF_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](#_ENREF_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](#_ENREF_1),[10](#_ENREF_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 > 100.000/mm3 platelets[[11](#_ENREF_11),[12](#_ENREF_12)] who have predictors of good response[[1](#_ENREF_1)]. In these patients, treatment should be started promptly, with the aim of achieving SVR to avoid LT or post-LT HCV recurrence[[1](#_ENREF_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](#_ENREF_1)].

Reviews on first generation PIs used in the pre- and post-transplant setting reported higher SVR rates versus 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](#_ENREF_13),[14](#_ENREF_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](#_ENREF_1)]. In patients awaiting LT, achieving SVR reduces the risk of graft reinfection and consequently is predictive of a reduced risk of retransplantation[[1](#_ENREF_1)]. The relationship between SVR and reduced liver-related mortality rate in LT has been shown in several studies[[15-17](#_ENREF_15)]. 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](#_ENREF_16)]. The risk of HCC and hepatic decompensation is also lower in patients achieving an SVR versus those who have failed treatment[[15](#_ENREF_15),[16](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_18)]. However, extending treatment to beyond 48 weeks might be a concern due to tolerability issues, with higher treatment discontinuation rates reported[[19-21](#_ENREF_19)]. 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](#_ENREF_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](#_ENREF_10),[22-24](#_ENREF_22)]. Therefore, virus eradication or an undetectable HCV viral load before LT dramatically improves patient prognosis[[1](#_ENREF_1),[5](#_ENREF_5),[7](#_ENREF_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](#_ENREF_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-week follow-up[[9](#_ENREF_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](#_ENREF_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](#_ENREF_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/wk/600 mg/d and escalated to the maximal tolerated dose, and 20 were untreated controls[[26](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_3),[28-30](#_ENREF_28)]. 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](#_ENREF_28)], while studies investigating treatment response in established hepatitis show SVR rates from 21%–67%[[30](#_ENREF_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 ≥ 2 being predictive of death[[31](#_ENREF_31),[32](#_ENREF_32)]. Severe aggressive HCV infection can occur within 6 mo of LT and is associated with a rapid progression to graft failure[[7](#_ENREF_7),[23](#_ENREF_23),[31](#_ENREF_31),[32](#_ENREF_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](#_ENREF_33),[34](#_ENREF_34)].

In a cohort study of 30 consecutive patients (77% genotype 1) with post-LT HCV recurrence, treated with 48 wks’ 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](#_ENREF_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](#_ENREF_34)].

Studies have reported improved SVR in post-LT CHC patients failing PEG-IFN-alpha2b and switched to PEG-IFN-α2a-based therapy[[35](#_ENREF_35)]; but *de novo* autoimmune hepatitis has also been reported with this switch of therapy[[36](#_ENREF_36)].

## Triple therapy regimens

Triple therapy is recommended in patients with histologically proven CHC and HCV genotype 1[[1](#_ENREF_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 wks’ 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](#_ENREF_37)].

### *TVR and BOC-based therapy*

A 12-week pilot study showed that TVR-based triple therapy was effective in post-LT patients with HCV genotype 1[[38](#_ENREF_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](#_ENREF_38)]. In a retrospective follow-up study, 5/9 patients completed the full 48 wks’ 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](#_ENREF_38)].

TVR has been used successfully for post-LT HCV treatment in combination with PEG-IFNα/RBV[[39-43](#_ENREF_39)], and with TAC[[44](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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 with immunosuppressants cyclosporine and tacrolimus were easily managed[[45](#_ENREF_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](#_ENREF_46)].

# 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](#_ENREF_10)]. Dose reductions and treatment discontinuation are required in > 50% of patients[[1](#_ENREF_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](#_ENREF_1),[9](#_ENREF_9),[10](#_ENREF_10),[49](#_ENREF_49),[50](#_ENREF_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](#_ENREF_1)]. Growth factors and transfusion are often required to allow effective IFN doses to be continued[[1](#_ENREF_1),[6](#_ENREF_6),[51](#_ENREF_51)].

In the post-LT setting, TVR and BOC exhibit hematologic toxicity, renal dysfunction and an increased risk of severe infections[[1](#_ENREF_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](#_ENREF_1)]. The new DAAs act on specific viral components[[52](#_ENREF_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](#_ENREF_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](#_ENREF_54),[55](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_60)].

A DAA-based IFN-free regimen is being investigated in an ongoing open-label phase 2 study; 24 wks’ 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](#_ENREF_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](#_ENREF_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 weeks’ 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](#_ENREF_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](#_ENREF_65)]. LT-associated costs are even higher (about €150000 annually)[[66](#_ENREF_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](#_ENREF_67)]. A US retrospective analysis in > 50000 HCV patients, compensated cirrhosis and ESLD led to 32% and 247% increases in treatment costs/month, respectively, versus no cirrhosis, independent of age and comorbidity[[18](#_ENREF_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](#_ENREF_24)]. Similar results from an observational, multicenter cost-of-illness study in Italy[[68](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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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**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** | **Immunosuppressant** | **Efficacy** | **Tolerability** | **Other** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Before liver transplantation | | | | | | | | | | |
| Curry *et al*[[56](#_ENREF_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](#_ENREF_56)] | 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](#_ENREF_56)] | 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](#_ENREF_56)] | 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 wks’ therapy |
| Rogers *et al*[[44](#_ENREF_56)] | 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](#_ENREF_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 |
| Pungapong *et al*[[42](#_ENREF_56)] | 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[[40](#_ENREF_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](#_ENREF_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](#_ENREF_56)] | 3 | Case report | BOC (800 mg q8h)/PEG-IFN/RBV | 19 days | | NS | CyA | NS | NS | Minor increased CyA concentrations, requiring dose adjustments |
| Schilsky *et al*[[48](#_ENREF_56)] | 3 | Case report | BOC (800 mg q8h)/PEG-IFN/RBV | 19 days | | 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](#_ENREF_56)] | 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](#_ENREF_56)] | 40 | OL study | SOF (400 mg)/RBV | 24 wks | | 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.