World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i19.5768

World J Gastroenterol 2015 May 21; 21(19): 5768-5777
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Hepatitis C: New challenges in liver transplantation

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Author contributions: Filipec Kanizaj T designed the study and was the primary author of this paper; Kunac N completed the literature review and contributed to the writing, design and revision of the paper.
Conflict-of-interest: No potential conflicts of interest relevant to this article were reported.

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Received: November 28, 2014
Peer-review started: November 28, 2014
First decision: January 22, 2015
Revised: February 28, 2015
Accepted: April 17, 2015
Article in press: April 17, 2015
Published online: May 21, 2015

Abstract

In an era of great achievements in liver transplantation, hepatitis C viral infection (HCV) remains an unsolved problem. As a leading indication for liver transplantation in Western countries, HCV poses a significant burden both before and after transplantation. Post-transplant disease recurrence occurs in nearly all patients with detectable pretransplant viremia, compromising the lifesaving significance of transplantation. Many factors involving the donor, recipient and virus have been evaluated throughout the literature, although few have been fully elucidated and implemented in actual clinical practice. Antiviral therapy has been recognized as a cornerstone of HCV infection control; however, experience and success are diminished following transplantation in a challenging cohort of patients with liver cirrhosis. Current therapeutic protocols surpass those used previously, both in sustained viral response and side-effect profile. In this article we review the most relevant and contemporary scientific evidence regarding hepatitis C infection and liver transplantation, with special attention dedicated to novel, more efficient and safer antiviral regimens.

Key words: Hepatitis C; Liver transplantation; Treatment protocols; Pegylated interferon; Ribavirin; Direct acting antivirals

Core tip: Extensive and revolutionary new data are currently emerging in the field of hepatitis C viral (HCV) treatment. Knowledge is changing faster than ever, although the treatment of HCV infection remains the most challenging problem in transplantation. In this article we report new insights into the actual knowledge of treatment opportunities in the pre- and post-transplant periods.

Filipec Kanizaj T, Kunac N. Hepatitis C: New challenges in liver transplantation. *World J Gastroenterol* 2015; 21(19): 5768-5777 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i19/5768.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i19.5768

GLOBAL BURDEN OF HCV RECURRENCE

As the leading indication for liver transplantation (LT) in Western Europe and the United States, hepatitis C

viral (HCV) infection has captured the attention of both basic scientists and clinicians throughout the years[1]. In comparison to non-HCV transplant recipients, those with an HCV infection have higher death and allograft failure rates, mainly due to disease recurrence[2]. The deleterious recurrence of HCV infection universally occurs in patients with detectable viremia at the time of transplantation, leading to cirrhosis in up to 30% of patients within 5 years after LT[3,4]. Among those patients, approximately 50% experience decompensation within 1 year of follow-up, which is extremely high compared to non-transplant HCV patients[1].

A variety of factors influencing disease recurrence and graft fibrosis progression have been evaluated, with only a few reaching high enough significance to be at least partially implemented in routine clinical practice[1,5,6]. Using antiviral therapy to successfully prevent HCV recurrence and treat established graft infections has been recognized to improve patient and allograft survival[2,7].

Until 2011 and the arrival of direct acting antivirals (DAAs), boceprevir (BOC) and telaprevir (TVR), a combination of pegylated interferon (pegIFN) and ribavirin (RBV), was the basis of HCV therapy[8]. Although the SVR rates have improved with the new regimens, unsatisfactorily high rates of adverse events and serious drug-drug interactions have diminished clinicians' enthusiasm[9,10]. With the emergence of new DAA drugs, promising results have been obtained in the field of HCV infection therapy[11]. Although there are few studies on HCV liver waiting list and post-transplant patients, the results show improved rates of virus eradication along with acceptable side-effect profiles and negligible drug-drug interactions[12,13].

PATHWAY FOR DISEASE RECURRENCE

HCV RNA remains detectable in almost all patients after liver transplantation, with pretransplant levels being reached as early as a few days postoperatively[3]. In contrast to the natural course of HCV infection, disease progression is accelerated in post-transplant patients[1]. Of those with disease recurrence, 10%-30% develop cirrhosis within 5 years and have diminished survival rates of 41% and 10% at 1 and 3 years, respectively[2,14]. The most detrimental pattern of disease recurrence is fibrosing cholestatic hepatitis (FCH), occurring in 7%-15% of recipients and leading to early graft failure, decompensation and death[1,15]. As disease recurrence involves the majority of HCV liver recipients, the impact of various factors influencing the rate and severity of disease progression has been widely evaluated. Several potential factors concerning the donor, the recipient, and the hepatitis C virus have been proposed and linked to reinfection, although few have achieved universal consensus throughout the literature[14].

Advanced donor age has been shown to negatively influence graft and patient survival in many studies, with even relatively young donors (< 50 years of age) experiencing a substantial risk[5,16-18]. There has been much debate in the literature regarding the impact of donor type on disease recurrence and overall survival. Those in favor of living donor liver transplantation (LDLT) mention the overall younger age of donors, better organ quality and shorter cold ischemia time as factors with a positive impact, whereas those favoring deceased donor liver transplantation (DDLT) hypothesize that intense hepatocyte proliferation after LT and optimized donor-recipient HLA matching may negatively impact disease recurrence[19-22]. Recently, two large studies showed that there is no difference in patient or graft survival or HCV recurrence with regard to donor type[21,22]. Concerning pretransplant recipient variables influencing the post-transplant course, those found to have negative impacts include female gender, advanced recipient age and liver disease severity prior to LT[1,2,5].

The interplay between the recipient's suppressed immune response and the resulting "undisturbed" viral replication is the principal difference between post-transplant patients and those with native liver disease. An evaluation of the benefits of the two main calcineurin inhibitors (CNIs) used in liver recipients, cyclosporine (CsA) and tacrolimus (Tac), gave no clear recommendations in terms of the preferential use of one over another[15,17,23,24]. Although the antiviral and antiapoptotic properties of CsA have been demonstrated to inhibit liver fibrosis and decrease disease severity, recent studies have counterbalanced those findings and necessitated further investigations[1,24]. With respect to the effects of immunosuppression on disease recurrence, multiple studies have shown negative impacts of corticosteroid boluses used in the treatment of acute cellular rejection episodes on hepatitis C viremia and graft fibrosis progression[23,25].

Along with the well-proven effect of the interleukin 28B (IL-28B) polymorphism on antiviral therapy success, studies have evaluated its parallel impact on fibrosis progression and patient and graft survival. The impact of both donor and recipient IL-28B genotype on post-transplant outcome was discussed in a study by Charlton *et al*[26] suggesting that the IL-28B TT genotype in the recipient was associated with more severe disease recurrence. An appealing concept of IL-28B genotype donor and recipient matching was consequently investigated, but until now it has not reached practical implementation[27,28].

HCV genotype 1 has been shown to adversely affect post-transplant outcome in multiple studies, and advanced donor age has been proven to have the most negative impact on disease recurrence severity[6,17,29]. Studies evaluating the pre- and post-transplant viral load lack general conclusions, and despite undetectable viremia at the time of LT, 55% of patients develop HCV recurrence[15,16,23,29,30]. It is possible that HCV exists in the liver or peripheral mononuclear cells,

and therefore, even in cases of undetectable serum HCV RNA, recurrence can occur. In a study by Vasuri *et al*[31] patients with high serum and tissue HCV RNA levels were shown to have more severe and earlier disease recurrence, with significantly lower survival rates. The practice of obtaining protocol biopsies 1 year after transplantation has been established in many transplant centers, and it has been demonstrated that greater necroinflammatory activity and the presence of fibrosis are risk factors for the development of graft cirrhosis[18,29,32-34]. In addition to histological analysis of the liver graft, a study by Ghabril *et al*[16] evaluated the explanted liver inflammatory grade. It was found that greater inflammatory activity, mainly periportal and portal hepatitis, strongly correlates with post-transplant fibrosis progression.

APPROACHES IN BATTLING DISEASE RECURRENCE

Along with the impact of the previously mentioned factors on disease recurrence and overall patient and graft survival, antiviral therapy (AVT) success rates appear to be one of the most important factors[7,29,30,35-39]. Although more complicated and harder to achieve in patients with liver cirrhosis or after LT, SVR was proven in several studies to slow graft fibrosis progression with an impact on the overall disease course[7,35]. More importantly, in addition to slowing down the rate of disease progression, SVR could potentially contribute to clinical remission and prolongation or even the avoidance of the need for LT[37]. In a randomized controlled trial (RCT) by Carrión *et al*[36] that evaluated the impact of AVT on liver fibrosis progression, SVR was the only variable independently associated with fibrosis regression/stabilization.

The main reason for the generally lower SVR rates in patients with liver cirrhosis and post-LT patients is poor AVT tolerability with substantially higher rates of serious adverse events (SAEs), leading to dose reductions and therapy discontinuation. Accordingly, patients with higher grades of liver cirrhosis [Child turcotte pugh (CTP) class B or C] experience the lowest SVR rates with frequent complications[38-40]. Multiple studies have confirmed that patients with more severe liver disease obtain lower SVR rates, with many of the studies noting that HCV genotype 1 is an additional negative contributor[1,30,37-40].

An issue specific to post-transplant patients is the effect of immunosuppression, possibly "blunting" the response to standard interferon based therapy[14]. In a recent meta-analysis, Rabie *et al*[41] found slightly higher SVR rates with the use of CsA compared to Tac, yet the heterogeneity of the studies and the need for larger well-established trials limited their ability to draw clear conclusions. Another predictor of SVR that was recently intensively evaluated was the IL-28B polymorphism, both donor and recipient genotypes of which were shown to affect the AVT success rate[26,42].

Attempts to minimize disease recurrence with pretransplant AVT first utilized the pegIFN and RBV combination, which was the main HCV therapeutic option until very recently. The frequent presence of pancytopenia and other manifestations of liver disease were the main obstacles to even initiating therapy in some patients[1,14,37,40]. The concept of a low accelerating dose regimen (LADR) was presented by Everson *et al*[37]. They treated 124 patients with a mean CTP score of 7.4 ± 2.3 with interferon alfa-2b or peginterferon alfa-2B plus RBV, achieving an end of treatment (ETR) response of 46% and SVR of 24%. Importantly, they found that 80% of patients who were HCV RNA negative at the time of LT lacked post-transplant recurrence, whereas those who were HCV RNA positive at the time of LT experienced universal infection recurrence. Overall disease recurrence was avoided in 26% of patients. Side effects, mainly cytopenias and complications of advanced liver disease, were commonly encountered, thus highlighting the need for caution and close supervision of the treated population.

In the first RCT of pretransplant treatment of HCV infection using pegIFN and RBV to prevent disease recurrence after LT, post-transplant clearance of HCV was achieved in 25% of patients, similar to the results found in previous studies[38]. The relapse rate of 50% was higher than that observed in previous studies, accentuating the need for therapy of adequate duration because those who received fewer than 8 wk of treatment universally relapsed. In contrast, the early virologic response (EVR) (undetectable serum HCV RNA or a 2 $\log_{10}$ or greater drop in HCV RNA at week 12 of therapy) was able to predict the likelihood of recurrence prevention. Although SAEs occurred with similar frequencies in the treated *vs* untreated groups (68% *vs* 55%, $P = 0.003$), the numbers of SAEs and infections were higher in the treated population, once again showing the detrimental effect of this therapeutic regimen in patients with advanced liver disease.

In 2011, with the arrival of new DAAs, the protease inhibitors boceprevir and telaprevir, optimism emerged regarding the treatment of patients with liver cirrhosis and those on liver transplant waiting lists. Despite the considerably higher SVR rates when combined with pegIFN-RBV in patients with genotype 1 and cirrhosis, further studies halted the wave of enthusiasm[1,8,10,43,44]. A large study including a cohort of patients with compensated cirrhosis and evaluating the safety profiles of DAAs showed an SAE rate of 40% and a 6.4% rate of death and severe complications, with a platelet count $\leqslant 100000/mm^3$ and serum albumin concentration < 35 g/L as indicators for high risk patients[45]. Currently, the general opinion is that triple therapy should be used only in patients with compensated cirrhosis and in well-experienced transplant centers[8,43,44].

A promising SVR rate of 69.6% in genotype 1b patients with advanced liver disease treated with TVR

Table 1 Data on new therapeutic protocol efficacy and safety in post-liver transplantation period

	Charlton *et al*[13]	Forns *et al*[68]	Pellicelli *et al*[69]
Patients (*n*)	40	104	12
Regimen	SOF + RBV	SOF + RBV + pegIFN	SOF + DCV
Patients with cirrhosis	40%	50%	75%
End of treatment response	100%	87%	100%
Sustained viral response 12	70%	62%	NA
Sustained viral response 24	70%	NA	NA
Serious adverse events	15%	33%	30%
Deaths	0	12.5%	25%

SOF: Sofosbuvir; RBV: Ribavirin; pegIFN: Pegylated interferon; DCV: Daclatasvir; NA: Not available.

was presented by Ogawa *et al*[46]. Indicators for the likelihood of achieving SVR included prior response to therapy, rapid viral response (RVR) (defined as undetectable HCV viral load at 4 wk of therapy) and favorable IL-28B genotype, as SVR was obtained in only 12.5% of patients with a prior null-response and the IL-28B TC/CC genotype. Almost all of the patients required RBV dose reductions due to anemia, which was the main adverse effect in addition to leuko/thrombocytopenia and dermatological disorders, leading to therapy discontinuation in 12.7% of cases.

In a multicenter study of 160 patients with liver cirrhosis treated with BOC and TVR, Saxena *et al*[9] analyzed the overall efficacy and SAE rate with regard to disease severity. SVR12 was achieved in 35% of patients with Child-Pugh (CP) $\geqslant$ 6, compared to 54% of those with CP = 5 (P = 0.02), with RVR and genotype 1b identified as predictors for SVR. An encouraging rate of 67% post-transplant SVR was achieved, mostly (80%) in patients who were HCV RNA negative for at least 5.5 wk prior to LT. SAEs subsequently leading to IFN dose reduction, growth factor use and transfusions were more frequent in the CP $\geqslant$ 6 group, thus requiring treatment discontinuation in 42% of patients (Table 1).

Recent results from the CUPIC study group of 511 patients with compensated cirrhosis revealed relatively high SVR rates of 74.2%, 40% and 19.4% in patients with a relapse, partial response and null response, respectively[47]. However, the high number of SAEs (49.4%), infections (10.4%) and deaths (2.2%) once again demonstrated the need for caution, even with the possibility of attaining positive SVR rates.

In addition to treating patients in the pretransplant period, two post-transplant strategies have evolved for preventing HCV disease recurrence[1,8,14,43,44]. Although there is the possibility of treating liver recipients in this phase with lower HCV RNA levels and in the absence of significant graft injury, the preemptive/prophylactic regimen has not yet achieved clinical implementation[8,43,44,48,49]. One of the reasons accounting for the lack of wider use of early post-transplant therapy is low patient eligibility, mainly due to cytopenias, renal impairment and severe debilitation. Even when treatment initiation is possible, patients in this vulnerable period experience frequent SAEs, leading to dose reductions, discontinuation and unsatisfying SVR rates[48,49].

The results obtained from the PHOENIX study verified the lack of benefit from prophylactic treatment[49]. With only 65% of patients able to complete therapy, SVR was achieved in 22.2% in the prophylactic group and in 21.4% of patients in the observation group, where treatment was started upon significant HCV recurrence (histological activity index $\geqslant$ 3 and/or fibrosis score $\geqslant$ 2). The results showed no clear benefit regarding HCV recurrence or patient or graft survival, thus lending no support to that strategy, at least until enough experience has been gained with these new regimens.

The first attempts to treat recurrent HCV infection after liver transplantation were made using a standard combination of interferon/pegylated interferon and ribavirin, with SVR rates reaching up to 40%[36,50-52]. A significant number of patients were not able to sustain full doses of the antivirals, and adverse events, mainly cytopenias, occurred frequently[14,36,50-52]. In a study by Angelico *et al*[50] in which 35% of patients required IFN dose reductions and only a minority tolerated full doses of RBV, significant anemia occurred in almost all of the patients. The importance of careful patient selection for both the AVT success rate and the minimization of adverse events was accentuated in a study by Carrión *et al*[36]. They grouped 81 patients into categories according to the liver fibrosis stage, showing that patients with severe recurrence (fibrosis stage 3-4, FCH) responded much worse (SVR 18.5%) compared to patients with mild recurrence (SVR 48%). In that study, AVT was shown to be the only independent variable associated with fibrosis improvement/stabilization (OR = 3.7, P = 0.009). A comprehensive multicenter study by Gordon *et al*[52] once again highlighted the importance of sustaining the full dose and duration of treatment. Of 125 patients treated with pegIFN-alfa-2b and RBV, only 58.4% completed 48 wk of therapy, achieving 55% SVR. The overall SVR rate was 28.8% and was significantly higher in patients with genotype 2/3 (55%) than with genotype 1 (23.8%) and in those who achieved RVR (83.3% *vs* 25.7%, P = 0.0098). Despite attaining a relatively high SVR in those who were able to complete the full treatment duration, adverse events occurred in almost all of the patients, with 65% of patients requiring either dose reduction or discontinuation.

To improve the relatively low SVR rates in genotype 1 patients with HCV recurrence, the protease inhibitors BOC and TVR were added to the standard dual therapy regimen[1,8,10,14,43,44]. A remarkable SVR rate increase (from 45% to 75%) was obtained, although a high

incidence of SAEs and significant drug-drug interactions necessitated careful patient selection and precise treatment supervision[43,44].

In a retrospective study of a cohort of patients treated with TVR, Werner *et al*[53] reported SVR24 in 5 of 9 patients treated, although the overall benefit diminished, with two-thirds of patients experiencing severe anemia requiring transfusions and growth factor administration.

A study of 60 patients treated with BOC and TVR published by Pungpapong *et al*[54] showed undetectable HCV RNA at week 24 of therapy in 67% of patients treated with TVR and 45% treated with BOC. Limited treatment efficacy was found in patients with HCV genotype 1a and IL-28B polymorphism CT or TT, but interestingly, no correlation existed between the on-treatment virological response and either the fibrosis stage or baseline HCV level. A major concern during the treatment was the universal need for dose reductions of pegIFN and RBV and the administration of hematologic growth factors and transfusions in more than half of the patients. The incidence of acute cellular rejection (5%) was similar to the rates in the published studies of dual antiviral therapy[55]. Frequent drug-drug interactions between BOC, TVR and CNIs were demonstrated, necessitating immunosuppressive dose reductions. With both treatments being substrates and inhibitors of CYP3A4/5 and the efflux pump P-glycoprotein, pharmacokinetic studies showed a 70-fold and 4.6-fold increase in the exposure to Tac and CsA, respectively, when they were administered with TVR, and a 17-fold and 2.7-fold increase in Tac and CsA exposure when administered with BOC[56,57].

A recent multicenter study by Coilly *et al*[58] presented ETR rates of 72% and 40% for patients treated with BOC and TVR, respectively, with an impressive ETR of 33% in patients with FCH. Although limited by the low number of enrolled patients (n = 37), EVR was shown to be the principal factor in achieving SVR. With EVR rates of 89% and 58% in patients treated with BOC and TVR, respectively, SVR12 was obtained in 71% of BOC- and 20% of TVR-treated patients.

Even more encouraging results were presented by Burton *et al*[59] demonstrating an SVR rate of 63% in patients treated with BOC plus TVR, proving EVR to be highly predictive of SVR. One-fifth of patients experienced a decline in hemoglobin to < 8 g/dL, with erythropoietin and packed red blood cells used in 81% and 57% of patients, respectively. Overall, 27% of patients required hospitalization, with death occurring in 9% of cases. Along with significant and potentially dangerous interactions with CNIs, adverse events were the main factor compromising the achievement of relatively high SVR rates, adding to the non-establishment of triple therapy in post-transplant disease recurrence.

NEW EFFICACIOUS AND SAFE THERAPEUTIC REGIMENS

With the approval of the NS5B nucleotide polymerase inhibitor sofosbuvir (SOF) in 2013, a brighter perspective finally appeared for HCV infected patients, especially for liver cirrhosis and post-LT patients[11]. Owing to its high efficacy, pangenotypic activity, high barrier to genetic resistance, rare drug-drug interactions and acceptable side-effect profile, sofosbuvir rapidly emerged as a savior in the treatment of patients with advanced liver disease[60-62].

In an open-label phase 2 study by Curry *et al*[12] the combination of SOF and RBV was assessed in preventing HCV recurrence after LT. They enrolled 61 patients with HCV of any genotype and cirrhosis on the LT waiting list due to hepatocellular carcinoma. SOF and RBV were administered for 48 wk, with 43 patients achieving undetectable HCV RNA at the time of LT. Of those patients, 70% achieved pTVR12 (defined as undetectable HCV RNA at 12 wk post-transplant in patients who had undetectable HCV RNA at their last assessment prior to LT), which led to an overall pTVR12 of 49%. It was demonstrated that the removal of the infected liver with the achievement of undetectable HCV RNA led to a low risk of recurrence, thus diminishing the significance of extrahepatic viral reservoirs. Nevertheless, a 23% rate of recurrence raised questions about the adequate duration of viral suppression prior to LT and the possibility of extending treatment to the post-transplant period[63,64]. Proving the safe side-effect profile of SOF, the adverse events most frequently encountered were fatigue (38%), headache (23%) and anemia (21%), and the discontinuation rate was low.

Jacobson *et al*[61] presented the results of 2 RCTs in which they evaluated the efficacy of SOF and RBV in the treatment of patients with HCV infections of genotypes 2 and 3. In the POSITRON trial, a blinded placebo-controlled study in patients (n = 207) for whom IFN antiviral regimen was not an option, an SVR12 of 78% was obtained after 12 wk of therapy. The second study, a blinded active-control FUSION trial of previously treated patients (n = 201), showed an SVR12 rate of 50% with 12 wk of therapy and 73% with 16 wk of therapy (P < 0.001). Both studies revealed lower SVR rates for genotype 3 patients and those with cirrhosis, with additional benefits achieved after treatment prolongation. Adverse events associated with RBV therapy (fatigue, insomnia, anemia) appeared more frequently in the group that received SOF and RBV, whereas other common adverse events occurred similarly in the treatment and placebo groups. There was no difference in the frequency of adverse events with regard to treatment duration or the presence of liver cirrhosis.

In contrast to IFN-free sofosbuvir regimens, Lawitz

et al[65] published the results of pegIFN-RBV plus SOF therapy in patients with genotype 2 or 3 HCV infections and liver cirrhosis. With an encouraging SVR12 rate of 89%, that combination appeared to be an effective option for treatment-experienced patients with liver cirrhosis who were able to receive IFN. Again, better SVR rates were obtained in genotype 2 than in genotype 3 patients (96% and 83%, respectively), with no significant difference in patients with *vs* without cirrhosis.

The combination of a second-wave NS3/4A protease inhibitor, simeprevir (SMV), plus SOF was evaluated in the COSMOS randomized trial[62]. A total of 167 patients were grouped according to their previous therapy experience and liver disease severity, and they were administered 150 mg of SMV and 400 mg of SOF once daily for 24 wk with or without RBV. A promising AVT success rate with an acceptable adverse event frequency was achieved because the SVR12 was 90% in patients with no or mild fibrosis (F0-2) and 94% in those with advanced fibrosis and cirrhosis.

Another two new DAAs, the NS5A replication complex inhibitor daclatasvir (DCV) and the NS3 protease inhibitor asunaprevir, were assessed in an all-oral therapy HCV genotype 1b study (HALLMARK-DUAL). Including patients with cirrhosis, the combination of 60 mg of daily DCV and 100 mg of twice daily asunaprevir for 12 wk produced an SVR12 rate in 82%-90% of patients, according to previous treatment experience and tolerability. Adverse events occurred in up to 7% of patients, leading to a negligible discontinuation rate, thus proving this IFN-free therapeutic regimen to be safe and effective in a difficult-to-cure patient population[66].

Data regarding the treatment of HCV recurrence after liver transplantation with new DAAs were scarce until Charlton *et al*[13] published a study of SOF and RBV treatment for patients with compensated infection recurrence. That prospective multicenter study enrolled 40 patients; 83% of the patients had a genotype 1 infection and 40% of patients had liver cirrhosis. On an intention-to-treat basis, after 24 wk of SOF and RBV therapy, SVR12 was achieved in 70% of patients, with undetectable HCV RNA observed in 97-100% patients at week 4 of treatment. Fatigue, diarrhea or headache occurred in approximately one-third of patients, and despite a slow dose escalation protocol, anemia precluded full ribavirin dosing in the majority of patients. No death, graft loss or rejection episodes occurred in the studied population. In addition to the safe administration of SOF, its exposure was only minimally altered by CNIs, and no net directional change in the trough levels of CsA or Tac were observed. Despite these findings, vigilant monitoring of the CNI concentration during and after treatment is recommended[13,67]. Possible limitations on the general acceptance of the highly effective and safe administration of SOF in patients with HCV recurrence may relate to the fact that, as in most pretransplant series, the studied population consisted of patients with well-compensated liver disease. In a compassionate use program providing SOF for patients with a severe recurrent HCV infection and FCH, Forns *et al*[68] evaluated 104 patients in which half of the patients had compensated or decompensated cirrhosis and the other half had FCH and early disease recurrence. An overall rate of treatment discontinuation of 30% and a high occurrence of death (12.5%) diminished the significance of the relatively high SVR12 rate of 62%.

Simeprevir and daclatasvir have also been evaluated in post-transplant HCV recurrence treatment, although until now only case reports and small patient series have been published. Pellicelli *et al*[69] treated 12 patients with severe HCV recurrence (n = 9) and FCH (n = 3) with a combination of SOF and DCV, with or without ribavirin. ETR was achieved in all 9 patients who completed the treatment, and undetectable HCV RNA proof was available for 5 patients at week 8 (n = 2) or week 4 after treatment (n = 3). Confirming the lack of significant drug-drug interactions, no adjustment of immunosuppressive drug dosage was necessary during the treatment. With 4 patients experiencing SAEs and 3 who died (25%), the authors strongly recommend that treatment be started at an early stage of HCV recurrence, thus avoiding the frequent complications of advanced liver disease.

In two case reports by Fontana *et al*[70,71] SVR was achieved in patients with FCH with either SOF plus DCV or pegIFN-RBV plus DCV therapy. Favorable safety profiles of SOF plus DCV were observed, along with negligible interactions with CNIs.

Successful DCV-based treatment of a patient with BOC triple therapy failure after liver transplantation was described by Reddy *et al*[72]. Although he responded to triple therapy, the patient remained HCV RNA positive, experienced serious adverse events and required immunosuppression dosage adjustment. After 2 wk of DCV and pegIFN/RBV therapy, he became HCV RNA negative and remained so for 12 wk after therapy completion.

Concerning experience with simeprevir use in post-transplant HCV recurrence, Campos-Varela *et al*[73] presented two HIV-HCV co-infected patients with dual (pegIFN-RBV) plus BOC based triple therapy failure after transplantation, respectively. SOF and SMV plus RBV therapy produced SVR12 in both patients, and the treatment was well-tolerated and no adjustment of immunosuppression was needed. More importantly, as demonstrated by CTP and the model for end stage liver disease (MELD) scores, the overall condition of the patients improved.

In a pilot study by Tanaka *et al*[74] 5 patients underwent 12 wk of SMV, pegIFN and RBV therapy as part of a preemptive dual therapy course. All of the patients completed the course without significant adverse events and with minimal CNI dose modifications. RVR was observed in 3 out of 5 patients, creating a positive basis for future larger

studies establishing simeprevir for post-transplant HCV recurrence therapy.

Compared to IFN-based regimens, except for their greater efficacy and shorter treatment duration, new IFN-free regimens have the most favorable side-effect profiles. Excellent treatment results with these new regimens are challenged by scarce data on the treatment of minimally decompensated liver transplant candidates (CTP C) due to unfavorable drug metabolism in hepatic failure and renal insufficiency.

CONCLUSION

With the evolution of new antiviral drugs and more precise and clear knowledge of HCV disease recurrence, promising results have begun to emerge in the complex field of liver transplantation. A substantial proportion of patients who are either ineligible for or poorly tolerate interferon-containing regimens experience rapid deterioration in their natural HCV infection course and upon HCV recurrence after transplantation. Highly effective and safe antiviral therapy regimens that have been extensively evaluated have the potential to prevent many HCV patients from undergoing the burden of transplantation and may provide benefits for liver recipients.

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P- Reviewer: Fourtounas C, Kita K **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Liu XM

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ISSN 1007-9327