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TOPIC HIGHLIGHT

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Hepatitis C virus reinfection after liver transplantation: Is there a role for direct antiviral agents?

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Abstract

Recurrence of hepatitis C virus (HCV) infection following liver transplantation (LT) is almost universal and can accelerate graft cirrhosis in up to 30% of patients. The development of effective strategies to treat or prevent HCV recurrence after LT remains a major challenge, considering the shortage of donor organs and the accelerated progression of HCV in LT recipients. Standard antiviral therapy with pegylated-interferon plus ribavirin is the current treatment of choice for HCV LT recipients, even though the combination is not as effective as it is in immunocompetent patients. A sustained virological response in the setting of LT improves patient and graft survival, but this is only achieved in 30%-45% of patients and the treatment is poorly tolerated. To improve the efficacy of pre- and post-transplant antiviral therapy, a new class of potent direct-acting antiviral agents (DAAs) has been developed. The aim of this review is to summarize the use of DAAs in LT HCV patients. PubMed, Cochrane Library, MEDLINE, EMBASE, Web of Science and clinical trial databases were searched for this purpose. To date, only three clinical studies on the topic have been published and most of the available data are in abstract form. Although a moderately successful early virological response has been reported, DAA treatment regimens were associated with severe toxicity mitigating their potential usefulness. Moreover, the ongoing nature of data, the lack of randomized studies, the small number of enrolled patients and the heterogeneity of these studies make the results largely anecdotal and questionable. In conclusion, large well-designed clinical studies on DAAs in HCV LT patients are required before these drugs can be recommended after transplantation.

Key words: Hepatitis C virus; Liver transplantation; Direct antiviral agents; Peginterferon/ribavirin; Immunosuppressive agents

Core tip: Considering the increasing shortage of donor organs and the accelerated progression of hepatitis C (HCV) in liver transplant recipients, the development of effective strategies to treat HCV recurrence are of paramount importance. The new classes of direct antiviral agents (DAAs) improved the results of antiviral therapy in HCV-infected immunocompetent patients. The aim of this review was to identify and summarize the potential benefit of DAAs in the liver transplant setting.

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INTRODUCTION

Since the discovery of hepatitis C virus (HCV) in 1989 as the causative agent of non-A, non-B hepatitis, impressive progress has been made in treating this infection. Currently available therapeutic strategies are mainly based on a combination of peginterferon (PEG-IFN) and ribavirin (RBV). This treatment succeeds in eradicating HCV in many chronically infected patients thereby reducing the risk of developing cirrhosis, liver cancer and the need for liver transplantation (LT). However, current therapies remain ineffective in some patients and are associated with significant toxicity in others. In particular, the treatment of HCV recurrence after LT remains disappointing and represents a major problem for most transplant programs.

Chronic HCV-induced end-stage liver disease is the leading indication for LT[1,2] while HCV graft reinfection is the major cause of allograft loss[3,4]. Indeed, the natural history of HCV infection in post-transplant recipients has an accelerated course compared with non-transplanted patients, resulting in early development of cirrhosis[5-16]. In addition, a subgroup of patients (about 2%-5%) develop fibrotic cholestatic hepatitis, a severe and aggressive form of HCV recurrence characterized by rapid progression to graft failure and death[8]. Once cirrhosis develops, the annual risk of hepatic decompensation is about 40%[8,10] and about 10%-25% of patients will die or require re-transplantation within five years post-transplantation[12]. Unfortunately, the outcome of retransplantation is poor and most transplant centers refuse to offer a second LT on this account[13]. Factors associated with graft loss in HCV-infected patients include host and viral factors[8,14,17-21] as well as immunosuppression that may facilitate viral replication[22-24].

Considering this scenario, effective strategies to treat or prevent post-transplant HCV recurrence are of paramount importance. Three approaches have been identified according to the timing of treatment: pretransplant antiviral therapy, only feasible in patients with compensated cirrhosis due to the frequent and severe treatment-related complications; post-transplant pre-emptive treatment; and treatment for established reinfection. This review addresses the treatment of post-transplant HCV focusing on the use of new antiviral drugs.

TREATMENT OF HCV IN TRANSPLANTED PATIENTS

In the post-transplant setting, HCV patients can be treated with a pre-emptive approach immediately following transplantation, or with a recurrence-based approach when liver damage is diagnosed. The advantages of pre-emptive or early post-transplant treatment are that serum HCV-RNA levels are characteristically low and significant histological graft damage is virtually absent. Although these factors predict a favorable response, this therapeutic approach is difficult to manage because of poor tolerability and reduced efficacy of the peginterferon/ribavirin combination[25,26]. Thus, the preferred approach is to delay antiviral treatment until histological evidence of recurrent post-transplant HCV-related chronic hepatitis is established. In this setting, the interferon (IFN) plus ribavirin combination for 12 mo is associated with an overall sustained virological response (SVR) of about 20% to 30%[27] while the PEG-IFN and RBV association leads to SVR rates of about 30%-45%[28-32]. Among many factors that could jeopardize the response to treatment[28-36], polymorphism of the *IL28B* gene encoding IFN plays a pivotal role. Indeed, it has been demonstrated that combination analyses of single nucleotide polymorphisms of *IL28B* in recipient and donor tissues and mutations in HCV RNA allow prediction of SVR to therapy[37,38]. Moreover, early virological response is the main predictor of SVR[39].

The recent introduction of direct-acting antivirals (DAAs), including protease, polymerase and other non-structural protein inhibitors, heralds a new era in HCV treatment[40]. At present, only boceprevir (BCV) and telaprevir (TLV) have been released and approved by the Food and Drugs Administration in May 2011 for immunocompetent patients in association with PEG-IFN and RBV (Table 1). Both drugs inhibit the same viral protein, namely NS3/4A, that is crucial for viral replication, and are more active against genotype 1 than other HCV genotypes[41,42].

Table 1 Current stage of development of direct antiviral agents

Inhibitors of the NS3/4A serine protease	
First-generation	
Boceprevir	Approved
Telaprevir	Approved
Faldaprevir	Active clinical development
Sovaprevir	Active clinical development
Asunaprevir	Active clinical development
Simeprevir	Active clinical development
Danoprevir	Active clinical development
Vaniprevir	Active clinical development
Second-generation	
MK-5172	Active clinical development
NS5A inhibitors	
Daclatasvir	Advanced clinical development
GS-5885	Active clinical development
ABT-267	Active clinical development
PPI-461	Active clinical development
MK-8762	Active clinical development
NS5B polymerase inhibitors	
Nucleos(t)ide inhibitors	
Sofosbuvir	Advanced clinical development
Mericitabine	Active clinical development
ALS-2200	Active clinical development
Non-nucleos(t)ide inhibitors	
Setrobuvir	Active clinical development
ABT-333	Active clinical development
GSK625433	Active clinical development

LITERATURE RESEARCH

We searched the following electronic databases: PubMed, MEDLINE, the Cochrane Library, EMBASE, Web of Science, and clinical trial databases for original studies

Table 2 Available data from the studies *in extenso* on the use of direct-acting antiviral agents in the post-liver transplantation setting

	Pungpapong *et al*[44]	Coilly *et al*[45]	Werner *et al*[46]	Werner *et al*[48]
Patients (*n*)	60	37	9	14
Baseline characteristics				
Regimen (*n*)				
TLV	35	19	9	14
BCV	25	18	0	0
Four-week lead-in phase	100%	100%	0%	0%
IS therapy (*n*)				
TAC	3	15	4	6
CSA	65	22	4	6
SIR	1	0	1	2
Fibrosis stage (*n*)				
FO-F2	31	20	6	7
F3-F4	38	17	3	7
Cholestatic hepatitis (*n*)	NA	6	1	NA
Results				
HCV-RNA negative				
Week 4	NA	51% (19/37)	44% (4/9)	43% (6/14)
Week 8	NA	NA	NA	NA
Week 12	91% (55/60)	73% (27/37)	89% (8/9)	71% (10/14)
Week 24	56% (24/43)	NA	NA	57% (8/14)
Week 48	NA	61% (17/28)	NA	50% (7/14)
Adverse events				
Hematological AEs				
Anemia	93%	92%	66%	71%
Leukopenia	77%	40%	22%	36%
Thrombocytopenia	12%	32%	44%	64%
Infectious complication	12%	27%	11%	14%
Renal insufficiency	38%	13%	11%	7%
Acute rejection	5%	NA	0%	7%
Dermatological toxicity	10%	5%	33%	NA
Hepatic decompensation	12%	NA	0%	7%
Death	3%	8%	0%	7%

BCV: Boceprevir; TLV: Telaprevir; HCV: Hepatitis C virus; IS: Immunosuppressive; TAC: Tacrolimus; CSA: Cyclosporine; SIR: Sirolimus; NA: Not available.

and all abstracts involving DAAs in the treatment of recurrent HCV after LT. Hypothetically, antiviral therapy in this context could be administered before LT to suppress viral replication and prevent recurrence. However, since DAAs are poorly tolerated by cirrhotic patients and there is a high risk of life-threatening complications, we selected only publications dedicated to post-transplant treatment[43]. Therefore, the use of DAAs in decompensated cirrhosis before LT should be discouraged for the time being.

RESULTS AND DISCUSSION

Five non-randomized studies and six abstracts on triple DAA therapy in the LT setting were found in the literature[44-54]. All of them pertain to the treatment of established HCV reinfection and no study was found on the use of DAA in post-transplantation prophylactic or preemptive therapy. The main results of these studies are summarized in Table 2. They present several methodological limitations that hamper their comparison, such as a small study population, lack of randomization, heterogeneous study design, different treatment schedules and follow-up periods.

In an open study, Pungpapong *et al*[44] reported data on 60 LT HCV-patients from three centers. Thirty-five patients were treated with TLV combined with PEG-IFN/RBV for 12 wk followed by PEG-IFN/RBV for 36 wk, and 25 with BCV plus PEG-IFN/RBV for 44 wk. All patients received a four-week lead-in therapy with PEG-IFN/RBV, and most of them (93%) were on maintenance immunosuppressive treatment with cyclosporine (CSA). In the TLV group, 30 out of 35 patients (86%) achieved undetectable HCV-RNA levels after an average of six weeks' treatment, whereas in the BCV group 12 out of 25 (48%) achieved undetectable HCV-RNA levels after an average of 11 wk. At the last follow-up (24 wk), 67% (14 out of 21) of TLV-treated patients and 45% (10 out of 22) of BCV-patients were HCV-RNA negative without viral breakthrough. However, the CSA dose was reduced in both groups to 70% of the original dose in the TLV group and 56% in the BCV group. Cytopenia was the most frequent adverse event requiring dose reduction of PEG-IFN and RBV or administration of hematological growth factors. Glomerular filtration rate declined in all patients, but none developed severe renal dysfunction. Hepatic decompensation occurred in two patients in the TLV group and in three in the BCV group. Biopsy-proven acute rejection developed in two TLV and one BCV patient. Two patients died from multiorgan failure due to sepsis in the TLV group and hepatic decompensation in the BCV group[44].

Coilly *et al*[45] evaluated the efficacy and safety of triple therapy (PEG-IFN/RBV + TLV or BCV) in 37 LT HCV genotype 1 patients from five French centers. They included patients who were naive (18), non-responders (14) or relapsers (5) to a previous course of dual therapy after LT. These patients received four-week lead-in therapy with PEG-IFN plus RBV followed by addition of BCV (800 mg *tid*) in 18 patients and TLV (750 mg *tid*) in 19 for 48 wk. The immunosuppressant regimen was CSA in 22 patients and tacrolimus (TAC) in 15. In the BCV group, the virological responses at weeks 4, 12 and 48 were 56%, 89% and 72%, respectively. In the TLV group, the virological responses at weeks 4, 12 and 48 were 47%, 58% and 40%, respectively. Negative viremia 12 wk after the end of treatment was obtained in 20% (1 out of 5) in the TLV group and in 71% (5 out of 7) in the BCV group. Sixteen patients discontinued the treatment (11 patients due to treatment failure, 5 to adverse events). The most common adverse event was anemia (50% in BCV group, 40% in the TLV group) requiring erythropoietin (EPO)

Table 3 Preliminary data on virological response during triple therapy in post-liver transplantation

	Verna *et al*[49]	Aqel *et al*[50]	McCashland *et al*[51]	Burton *et al*[52]	Kwo *et al*[53]	de Oliviera *et al*[54]
Patients (*n*)	101	23	10	12	7	6
Regimen						
BCV	10	23	0	0	0	0
TVL	91	0	10	12	7	6
Four-week lead-in phase	96%	100%	NA	100%	100%	NA
Fibrosis						
F0–F2	58	NA	7	8	5	NA
F3–F4	43	NA	3	4	2	NA
Cholestatic hepatitis (*n*)	10	NA	NA	NA	7	NA
IS therapy						
TAC	23	0	0	0	2	6
CSA	67	23	10	12	5	0
HCV genotype	1	1	1	1	1	1
HCV-RNA negative						
Week 4	70% (64/92)	43% (10/23)	22% (2/9)	92% (11/12)	29% (2/7)	NA
Week 8	78% (61/78)	NA	NA	NA	71% (5/7)	NA
Week 12	79% (68/86)	NA	100% (3/3)	NA	NA	33% (1/3)
Week 24	NA	17% (4/23)	100% (1/1)	NA	NA	NA

BCV: Boceprevir; TLV: Telaprevir; HCV: Hepatitis C virus; IS: Immunosuppressive; TAC: Tacrolimus; CSA: Cyclosporine; SIR: Sirolimus; NA: Not available.

administration or red blood cell transfusions. Infection was observed in ten out of 37 patients (27%), three of whom died from septic shock. This study also showed that a reduced dose of calcineurin inhibitors was needed. In the BCV group, the doses of CSA and TAC were reduced by 2-fold and 5-fold, respectively; while these reductions were 3-fold and 23-fold in the TLV group, respectively.

In a study by Werner *et al*[46] nine HCV-infected LT patients were treated with a combination of TLV, PEG-IFN and RBV in association with tacrolimus (TAC; 4 patients) or cyclosporine A (CSA; 4 patients) or sirolimus (1 patient), reporting data on efficacy and safety after 12 wk of treatment. At weeks four and 12, four (44%) and eight (89%) patients respectively were found to be HCV-RNA negative. However, two patients dropped out before completion of 12-week treatment because of side-effects. In one case, the discontinuation of antiviral treatment was not followed by a relapse of viral replication and this patient was still HCV-RNA negative at the end of the study. Cytopenia requiring RBV dose reduction was observed in about 33% of cases. Use of EPO or blood transfusion, or administration of granulocyte colony-stimulating factor, was needed in about 66% of cases. Moreover, patients treated with TAC experienced more side-effects and prolonged hospitalization. Patients with a CSA immunosuppression regimen needed a 2.5-fold dose reduction, whereas TAC patients required a much greater dose reduction (22-fold). Therefore, the use of DAAs hampered the management of immunosuppressant drug trough levels. Werner *et al*[47] recently reported the SVR at 24 wk after the end of treatment, showing a HCV-RNA negative outcome in 5 of the 9 patients.

In an even more recent published study, Werner *et al*[48] analyzed 14 HCV-infected LT patients treated with a combination of TLV, PEG-IFN and RBV. In this study, a SVR at 24 wk after end of treatment was observed in 5 out 14 patients (36%). Three further patients obtained HCV-RNA negativization during follow-up with a possible scenario showing an SVR of 57%.

The preliminary results, only presented in abstract form, show the same methodological drawbacks as the three full-length studies reported above. In addition, the reported data are preliminary, often related to ongoing studies. The results of these reports are summarized in Table 3.

In the largest currently ongoing multicenter study in the United States[49], 101 LT HCV patients were treated with triple therapy after lead-in with PEG-IFN and RBV. HCV-RNA negativization was obtained in 70%, 78% and 79% of patients, after 4, 8 and 12 wk of treatment, respectively. Concerning the adverse events, 49% of patients required transfusions because of severe anemia and 32% developed a worsening of renal function. Hematological growth factors were used in 86% of cases and PEG-IFN and/or RBV dose reduction was needed in 27% and/or 78% of cases, respectively. Hospitalization was required in 21% of cases, two patients experienced rejection and two patients died during treatment.

After a four-week lead-in phase study with PEG-IFN and RBV, Aqel *et al*[50] added BCV to 23 LT HCV genotype 1 patients. Ten (43%) achieved a complete virological response after four weeks and four of them continued to be negative at week 24. All patients required growth factors (EPO, granulocyte colony-stimulating factor) support for hematological adverse events.

A further ongoing US single center study[51] reported the preliminary results of a small group of LT patients with recurrent HCV treated for a maximum of 24 wk with PEG-IFN/RBV plus TLV. After a four-week treatment, a virological response was documented in two out of nine patients (22%), but only four patients were HCV-

RNA negative, three after 12 wk of treatment and one after 24 wk. Concerning adverse events, 20% of cases experienced anemia, 10% suffered leukopenia, and 20% had depression.

Burton *et al*[52] evaluated TLV in 12 LT HCV genotype 1 patients after a four-week lead-in phase with PEG-IFN and RBV. Triple therapy was administered for 12 wk, then all patients received an additional 36-wk period with PEG-IFN/RBV only. By week four, the viral load became undetectable in 11 out of 12 patients (91%). Treatment was withdrawn in two patients because of a presumed resistance to TLV with a rise of viremia. As far as side-effects are concerned, 42% patients required blood transfusion and 25% were hospitalized.

Another two very small series studies of genotype 1 HCV LT patients[53,54] showed virological response rates ranging from 33% to 100% after 12 wk of PEG-IFN/RBV plus TLV. Unfortunately, the number of patients achieving 12-wk of treatment is not reported.

It should be pointed out that the results of two phase 3 ongoing clinical trials on TLV are expected, one performed in six European countries (clinicaltrials.gov: NCT01571583), one in 22 United States centres (clinicaltrials.gov: NCT01467505).

The data about other DAAs in the transplant setting are very few. It is worth mentioning that there are only two case reports on the use of a new potent HCV replication inhibitor named daclatasvir in the treatment of post LT recurrent cholestatic hepatitis C[55,56]. Daclatasvir was administered for 24 wk in association with PEG-IFN/RBV or with sofosbuvir, a potent oral nucleotide analogue inhibitor of HCV polymerase activity, respectively. Interestingly, a complete SVR without serious adverse events was obtained in both cases. Moreover, there are two ongoing phase 2 studies about sofosbuvir and RBV and/or ledispavir in HCV post-transplanted patients (clinicaltrials.gov:NCT01779518; clinicaltrials.gov: NCT01938430).

There are several limitations to the interpretation of the few available data on the use of DAAs in the LT setting. Most studies refer to genotype 1 patients and lack of SVR, making it difficult to assess the overall treatment efficacy and compare PEG-IFN/RBV dual treatment and triple therapy regimens. Moreover, there are no comparative data on BCV-based and TLV-based therapy. In addition, tolerability and the risk of severe adverse events represent major concerns in the use of DAAs in LT. It is well known that the tolerability of the standard therapy based on PEG-IFN/RBV in LT patients is poor. In particular, hematological toxicity leads to a dose reduction in almost 70% of patients and premature termination of treatment in almost 30%[57]. Moreover, there are some reports that antiviral therapy might increase the risk of acute graft rejection[26,58]. In this context, the addition of DAAs could increase the incidence and severity of side-effects, thereby reducing the applicability of this new therapeutic strategy. Indeed, a bone marrow suppressive effect of TLV and BCV could amplify RBV- and PEG-IFN-induced anemia, neutropenia and thrombocytopenia[59]. In addition, TLV and BCV cause several adverse dermatological events, such as generalized pruritus with eczematiform lesions and anorectal disorders[60,61]. These data suggest careful monitoring and management of LT patients under treatment with triple antiviral therapy.

A further concern in the use of DAAs in LT is their interaction with calcineurin inhibitors (CSA and TAC). TLV and BCV are both CYP3A4 substrates and inhibitors and have the potential to saturate or inhibit P-glycoprotein in the gut, increasing calcinineurin inhibitor levels[62]. In healthy volunteers, evaluation of the effect of TLV and BCV on the pharmacokinetics of a single dose of CSA and TAC showed an increase in maximum plasma concentration (Cmax). The increase in Cmax of CSA and TAC after a single dose of TLV was about 1.4-fold and 9.3-fold, respectively[63], whereas a single dose of BCV increased the Cmax of CSA and TAC by 2-fold and 9.9-fold, respectively[64]. Coilly *et al*[65] also reported an estimated oral clearance reduction of 50% with CSA and about 80% with TAC.

CONCLUSION

Based on these scant preliminary results, it is difficult to offer any guidelines on the use of DAAs, mainly represented by TLV and BCV, in LT patients as the available data are neither consistent nor conclusive. DAA efficacy in terms of SVR cannot be quantified, nor can their adverse event profile be ascertained in the post-LT setting. In addition, the potential predictors of SVR have not yet been identified. However, the lack of clinically apparent drug interactions between calcineurin inhibitors and daclatasvir, combined with an SVR in both patients treated to date offers an exciting and effective prospect for patients with HCV recurrence after LT. Given the potential clinical benefits, hard clinical data on the effects of these new potent HCV inhibitors in patients with post-LT recurrence of HCV infection are urgently needed.

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