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Direct Antiviral Agents for the Treatment of Hcv Reinfection after Liver Transplantation

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Abstract

Recurrence of hepatitis C virus (HCV) infection after liver transplantation (LT) is almost universal and leads to cirrhosis in up to 30% of patients by five years. Considering the increasing shortage of donor organs and the accelerated progression of HCV in transplant recipients, the development of effective strategies to treat or prevent HCV recurrence are of paramount importance. Therapy with pegylated–interferon plus ribavirin, although less efficacious than in immunocompetent patients, is currently the treatment of choice of LT recipients with histologically proven recurrence of hepatitis C. However, this combination therapy results in a sustained virological response in around 30-45% of patients and is poorly tolerated. The new classes of potent and direct-acting antiviral agents (DAAs) will certainly improve the results of pre- and post-transplant antiviral therapy. The aim of this review is to identify and summarize the experience with the use of direct-acting antivirals in LT HCV patients. PubMed, the Cochrane Library, MEDLINE, EMBASE and Web of Science databases were searched for this purpose. To date, there are no published clinical studies on this topic and the only available data are in abstract form. The heterogeneous study designs and populations, the small number of enrolled patients, the different treatment schedules and follow-up periods and the ongoing nature of the reports make the results largely inconclusive or even anecdotal. In conclusion, the use of DAAs in HCV liver transplanted patients cannot be recommended until well designed large clinical studies will be performed.

Keywords: Liver transplantation; Hepatitis C virus infection; Direct-acting antiviral agents

Introduction

Chronic hepatitis C virus (HCV) infection is one of the most frequent causes of cirrhosis and represents the leading indication for liver transplantation (LT) in the USA and in many European countries [1,2]. Unfortunately, HCV infection after LT is an almost universal phenomenon in HCV-RNA positive candidates, representing a serious threat to the success of the transplant [3,4].

The natural history of HCV infection in post-transplant recipients is variable but generally more rapid and aggressive compared to not transplanted patients. A subgroup of transplanted HCV (about 1-9%) develop a fibrotic cholestatic hepatitis, characterized by a rapid progression to graft failure and death [5], while the majority of patients (about 70%) develop acute and then chronic hepatitis [6,7]. In contrast to the natural history of primary infection, liver disease progresses more rapidly in HCV recipients, with a progression to cirrhosis in 25-30% of patients within 5-7 years after surgery [8-11]. Furthermore, about 40% will develop hepatic decompensation within one year after the diagnosis of cirrhosis [8,10]. Therefore, the majority of HCV transplanted recipients suffer an inexorably poor outcome: about 10-25% will die or require re-transplantation within 5 years post-transplant [12]. Unfortunately, the results of retransplantation in these patients are disappointing, limited by the high likelihood of a further rapid HCV recurrence [13]. As a result, the overall and graft survival of transplanted patients with HCV infection is significantly lower than that of patients without hepatitis C [14-16].

There are many factors associated with disease and graft injury progression in patients with HCV recurrence after LT, including virological, donor and host characteristics, but for most of them the role is controversial. A high HCV load (>1 MEq/L) before transplantation, HCV genotype 1b [8,17,18] older age [19], female sex [14], race and severity of disease before LT [20] are all frequently associated with severity of HCV recurrence, fibrosis progression and a poor outcome. Similarly, donor factor like older age [18], allograft fat content and prolonged warm ischemia time are all related to poor outcome [21]. In any case, the immunosuppressed status is the most important factor in the evolution towards chronic hepatitis and cirrhosis. The overall immunosuppression level and/or dramatic changes in immunosuppression probably facilitate viral replication and the outcome of HCV recurrence [22].

Considering the increasing shortage of donor organs and the accelerated progression of hepatitis C in transplant recipients, the development of effective strategies to treat HCV-recurrence are of paramount importance.

Treatment of HCV Transplanted Patients

Higher viral load, cytopenia and some degree of renal insufficiency make the treatment of HCV transplanted recipients more difficult than in immunocompetent patients. In addition, many transplanted HCV patients are previous non-responders to pre-LT antiviral therapy [23].

In order to reduce the impact of HCV recurrence on graft and patient survival, several treatment strategies have been evaluated. Antiviral therapy could be administered before transplantation to suppress viral replication and reduce the risk of recurrence. However, the tolerability of this approach is poor; therefore it is applicable only

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in subjects with compensated cirrhosis which usually represent a minority [24].

After LT, patients can be treated immediately following transplantation (pre-emptive approach) or when chronic hepatitis is diagnosed (recurrence-based approach). The former allows therapy to be initiated within the first 4-6 weeks, when serum HCV-RNA levels are characteristically low and before the presence of significant histological graft damage. However, several studies demonstrated that antiviral therapy with IFN immediately post-transplant is difficult to manage and that the efficacy is poor [25,26]. Consequently, the better current approach is to initiate antiviral treatment in the presence of histological signs of HCV recurrence. Combination therapy of interferon (IFN) and ribavirin (RBV) for 12 months has been associated with an overall sustained virological response (SVR) of about 20 to 30% [27], while the more recent standard therapy with PEG-IFN and RBV leads to SVR rates of about 30-45% [28-32]. Among the many factors that could influence the treatment response [28-36] (Table 1), the polymorphism of IL28B gene, which codes for IFN, plays a pivotal role especially in patients with genotype 1 [37,38]. In addition early virological response (EVR) is the principal predictive factor of SVR [39].

New Strategies

Recently, several direct-acting antiviral drugs such as protease inhibitors, polymerase and other non-structural protein inhibitors, named direct antiviral agents (DAAs), have been developed as new treatment for HCV. At the moment, only Boceprevir (BCV) and Telaprevir (TLV) have been released and approved for immunocompetent patients in association with pegylated –IFN (PEG-IFN) and RBV. They inhibit the same viral protein, named NS3/4A, which is crucial for viral replication. Due to their molecular structure, these drugs are more active against genotype 1 than against other HCV genotypes [40,41].

In order to identify clinical studies involving DAAs in the treatment of recurrent hepatitis C after LT a literature search was performed in the following electronic databases: PubMed, MEDLINE, the Cochrane Library, EMBASE and Web of Science [42].

Results

The results of literature search showed that there is nothing published yet in the literature but one paper on triple therapy in LT setting using DAAs [43].

As far as the administration of antiviral treatment before transplantation is concerned, DAAs has been evaluated in patients with decompensated cirrhosis. But it is unknown if this treatment is able to reduce HCV recurrence after LT. In addition, it seems that the tolerability is poor and there is a high risk of life-threatening complications [40].

After LT, almost all preliminary results have been disclosed in abstract form and exclusively concern established HCV reinfection of the graft [44-51]. To the best of our knowledge there are no data about the use of DAAs in post-transplantation prophylactic or pre-emptive therapy.

So far, the available clinical experiences on the use of DAAs in LT HCV recipients are inconsistent and hampered by major methodological drawbacks, such as small study population, heterogeneous study design, different treatment schedules and follow-up periods, ongoing nature of data. In addition essential information such as the timing of treatment in respect to LT is often lacking. Keeping in mind these major limitations, the results of these few reports have been summarized in tables 2 and 3.

In the only study published in extenso, Werner et al. [43] treated 9 HCV-genotype 1 infected LT patients 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). The Authors reported efficacy and safety data after 12 weeks of treatment. At week 4 and 12, 4 (44%) and 8 (89%) patients respectively, were found to be HCV-RNA negative. However, two patients dropped out before the 12 week treatment period because of side effects even though in one case the discontinuation of antiviral treatment did not cause a relapse of viral replication and this patient was still HCV-RNA negative at the end of the study period. Two-thirds of patients developed cytopenia requiring RBV dose reduction, use of erythropoietin (EPO) or blood transfusion, or administration of granulocyte colony-stimulating factor (GCS-F). Moreover, patients treated with TAC experienced more side effects and more hospitalization. A reduction of individual dose of immunosuppressant drugs was necessary in all patients with a mean daily reduction dose of 2.5-fold and 22-fold for CSA and TAC, respectively. Therefore, the maintenance of stable through level of immunosuppressant emerges as a principal issue in treating transplanted patients with DAAs.

In the largest multicenter ongoing study in the USA [44], 61 LT HCV patients were treated with TLV after lead-in therapy with PEG-IFN and RBV. HCV-RNA negativization was obtained in 63% and 72% of patients, after 4 and 12 weeks of treatment, respectively. No data on both end-of treatment and SVR were reported. Moreover, 10 patients

Author	Predictive factors in univariate analysis	Predictive factors in multivariate analysis	SVR
Dumortier [28]	Completion of therapy, genotype non-1, VR at 3 months	NA	45%
Biselli [29]	VR at 1 and 6 months	NA	45%
Berenguer [30]	Use of EPO, VR at 3 months, adherence to therapy	VR at 3 months	50%
Nuemann [31]	NA	Baseline viremia < 1.000.000 UI/ml	36%
Sharma [32]	Low baseline viremia, higher dose of antiviral, longer therapy duration, EVR, EPO, anemia	None	37%
Crespo [33]	IL28B CC genotype with either low VL, young donor age, cyclosporine A -based immunosuppression		69%
Picciotto [34]	HCV genotype 2, higher dose of antivirals, absence of cirrhosis	HCV genotype 2, total dose PEG-IFN	28%
Oton [35]	Baseline HCV RNA, 2-4 years after LT, VR at 1-3 months	Baseline HCV RNA, 2-4 years after LT, VR at 1-3 months	44%
Roche [39]	EVR, completion of treatment, VL before therapy, genotype non-1	EVR	38%

Abbreviations: SVR: Sustained Virological Response; HCV: Hepatitis C Virus; RNA: Ribonucleic Acid; LT: Liver Transplantation; VR: Virological Response; PEG-IFN: Pegilated-interferon; NA: Not Available; EVR: Early Virological Response; EPO: Erythropoietin; IL28B: Interleukin 28B; VL: Viral Load

Table 1: Predictive factors associated with SVR.

	Werner [43]	Burton [44]	Aqel [45]	Pungpapong [46]	Coilly [47]	McCashland [48]	Burton [49]	Kwo [50]	de Oliviera [51]
Patients[n]	9	61	23	28	25	10	12	7	6
Regimen - BCV - TVL	 0 9	 0 61	 23 0	 0 28	 14 11	 0 10	 0 12	 0 7	 0 6
4 week lead-in phase	0%	NA	100%	NA	76%	NA	100%	100%	NA
Fibrosis [Ishak score]	NA	43% [>3]	NA	NA	84% [>3]	30% [>3]	83% [> 2]	29% [>3]	NA
Cholestatic hepatitis	11%	10%	NA	NA	16%	NA	NA	NA	NA
IS therapy - Tacrolimus - Cyclosporine	. 44% 44%	 27% 63%	 0 % 100%	 0 100%	 60% 40%	 0 100%	 0 100%	 27% 63%	 100% 0
HCV genotype	1	1	1	1a	1	1	1	1	1
HCV-RNA negative Week 4 Week 8 Week 12 Week 24	 44% [4/9] NA 89% [8/9] NA	 63% [28/44] NA 72% [21/29] NA	 43% [10/23] NA NA 17% [4/23]	 15% [4/26] NA 68% [13/19] 55% [6/11]	 44% [11/25] NA 76% [19/25] NA	 22% [2/9] NA 100% [3/3] 100% [1/1]	 92% [11/12] NA NA NA	 29% [2/7] 71% [5/7] NA NA	 NA NA 33% [1/3] NA

Abbreviations: BCV: Boceprevir; TLV: Telaprevir; HCV: Hepatitis C Virus; IS: Immunosuppressive; NA: Not Available

Table 2: Preliminary data about virological response during triple therapy in post-liver transplantation.

	Werner [43]	Burton [44]	Aqel [45]	Pungpapong [46]	Coilly [47]	McCashland [48]	Burton [49]	Kwo [50]	de Oliviera [51]
- Hematological AEs	66%	100%	NA	100%	100%	50%	50%	100%	NA
- Skin rash [mild]	33%	NA	NA	11%	NA	0%	0%	100%	17%
- Kidney failure	11%	33%	NA	NA	4%	NA	58%	NA	NA
- Death	0%	3%	NA	4%	8%	NA	NA	NA	17%
- Acute rejection	0%	3%	NA	7%	0%	0%	0%	0%	NA
Management									
- RBV reduction	78%	46%	NA	82%	52%	100%	83%	100%	NA
- EPO	66%	NA	NA	68%	92%	NA	61%	86%	NA
- Blood transfusion	66%	37%	NA	39%	8%	21%	56%	86%	NA
- Growth factor	22%	77%	100%	14%	NA	NA	NA	86%	NA
- Hospedalized	44%	18%	NA	14%	NA	NA	25%	NA	17%

Abbreviations: AEs: Adverse Events; RBV: Ribavirin; EPO: Erythropoietin; NA: Not Available

Table 3: Preliminary data about adverse events and their management during triple therapy in post liver transplantation.

(16%) prematurely stopped treatment because of an early virological failure in 6 and severe adverse events in 4. During triple therapy 37% of patients required transfusions and 33% developed renal failure. Growth factors were used in 77% and RBV dose reduction was needed in 46%. Hospitalization was required in 18% and 2 patients died during treatment for sepsis and hepatorenal syndrome, respectively.

Aqel et al. [45] treated 23 genotype 1 LT HCV patients with triple therapy (BCV+PEG-IFN+RBV) after a 4-week lead-in phase with PEG-IFN and RBV. Ten patients (43%) achieved a complete virological response after 4 weeks and 4 of them continued to be negative at week 24. All patients required growth factors support for haematological adverse events.

Pungpapong et al. [46] enrolled 28 LT patients with recurrent HCV infection to be treated with TLV plus PEG-IFN and RBV for 24 weeks. HCV-RNA negativization was obtained in 15%, 68% and 55% of cases after 4, 12 and 24 weeks, respectively. Severe adverse events included 2 cases of acute rejection and 1 death due to sepsis. As usual, cytopenia was extremely common, requiring EPO in 19 patients, blood transfusion in 11 and G-CSF in 4. In addition, dose reduction was required both for PEG-IFN (18 patients) and RBV (23 patients).

In five French LT Centres [47] an ongoing study analyzed the effect of triple therapy (PEG-IFN/RBV + TLV or BCV) in 25 LT patients with HCV genotype 1 both naives and non responders to a previous course of dual therapy after LT. These patients received 4 week lead-in PEG-IFN plus RBV followed by addition of BCV (800 mg tid) in 14 patients and TLV (750 mg tid) in 11. The immunosuppressant regimen was CSA in 15 patients and TAC in 10. Mean follow-up was about 20 weeks. A virological response was observed in 6 BCV patients (43%) and 5 TLV patients (45%) after 4 weeks and in 11 BCV patients (79%) and 8 TLV patients (73%) after 12 weeks. Two patients died (1 TLV, 1 BCV) for sepsis. Most common side effect was anemia (64%) so that about 90% in each group received EPO. Even in this series the dose of immunosuppressant drugs needed to be reduced, in particular in TLV patients.

The preliminary results obtained in a further group of 10 patients with recurrent hepatitis C after LT treated for a maximum of 24 weeks with PEG-IFN/RBV plus TLV in an ongoing US single centre study [48] showed a 4 week virological response of 22% (2 out of 9). The three patients who completed 12 weeks of therapy were all HCV-RNA negative as well as the only patient who reached week 24. The only reported data on adverse events were anemia (20%), leukopenia (10%) and depression (20%). No information on their severity was described.

Burton and Everson [49] evaluated the effect of the introduction of TLV after a 4-week lead-in phase with PEG-IFN and RBV in 12 LT patients with HCV genotype 1. Patients were treated for 12 weeks with triple therapy and then all patients received an additional 36 week period with PEG-IFN/RBV. By week 4, 11/12 (91%) patients reached an undetectable viral load even if two cases of resistance to TLV with a

rise of viremia were reported. About side effects, 42% patients required blood transfusion and 25% were hospitalized.

Other 2 very small series (less than 10 patients each) [50,51] analyzed the effect of the association PEG-IFN/RBV with TLV in transplanted patients with HCV genotype 1. The rates of virological response at 12 weeks ranged from 33 to 100%, but it is not clear how many patients completed 12-weeks of treatment.

To complete the description of available data on DAAs in LT setting, it is worth mentioning the use of a new potent replication inhibitor of HCV named dataclatasvir in association with PEG-IFN and RBV for 24 weeks in a single patient who developed recurrent cholestatic hepatitis C after liver retransplantation obtaining a complete SVR without serious adverse event [52].

From these preliminary data, tolerance and the risk of severe adverse events emerges as a major concern in the use of DAAs in LT patients. LT patients are particularly exposed to several side effects due to the standard therapy based on PEG-IFN/RBV, in particular to haematological toxicity leading to a dose reduction in almost 70% of patients and premature termination in almost 30% [53]. In addition, it is not completely understood if antiviral treatment in transplanted patients might increase the risk of acute rejection [26,54]. Consequently, the addition of a third drug, such as DAAs, could increase the incidence and severity of side effects thus reducing the applicability of this new therapeutic strategy. Indeed, in non transplanted patients it has been shown that RBV-induced anemia as well as PEG-IFN associated neutropenia and thrombocytopenia could be exacerbated by the addition of TLV and BCV, probably with a mechanism leading to a bone marrow suppressive effect [55,56]. Moreover, TLV and BCV are specifically associated with several adverse dermatological events, like generalized pruritus with eczematiform lesions and anorectal disorders [57,58]. These data suggest a careful monitoring and management of LT patients under treatment with triple antiviral therapy.

One of the major problem in the use of DAAs in LT is represented by interaction with immunosuppressive drugs, in particular with calcineurin inhibitors both cyclosporine (CSA) and tacrolimus (TAC). CYC and TAC are substrate of both cytochrome P450A 3A (CYP3A), the primary enzyme responsible for their metabolism and P-glycoprotein (P-gp), a transmembrane transporter. TLV and BCV are both CYP3A4 substrates and inhibitors and have the potential to saturate or inhibit P-gp in the gut, so they could increase calcinineurin inhibitor levels and the systemic exposure to these agents [59].

Garg et al. [60] evaluated the effect of TLV on the pharmacokinetic of a single dose of CSA and TAC in healthy volunteers. CSA maximum observed plasma concentration (Cmax) increased about 1.4 fold, the area under the curve (AUC) increased approximately 4.6 fold and mean t1/2 increased 4-fold. The effect was greater with TAC: dose normalized Cmax increased about 9.3 fold, AUC increased approximately 70-fold and the main t1/2 approximately 5-fold. Hulskotte et al. [61] demonstrated that concomitant BCV increased the AUC and Cmax of CSA of 2.7 and 2.0 respectively and increased the AUC and Cmax of TAC of 17 and 9.9, respectively. Coilly et al. reported an estimated oral clearance reduction by 50% with CSA and about 80% with TAC [62,63]. It cannot be excluded that in transplant recipients the potential interactions between calcineurin inhibitor and TLV or BCV could be higher and more variable than that seen in healthy volunteers, thus reducing their potential use in HCV recurrence after LT.

Conclusion

On the basis of these scanty data it is difficult to draw any conclusion. The few and preliminary data on the use of DAAs in LT patients are neither consistent nor conclusive. Due to the lack of consistent data, it is not possible to quantify the efficacy in terms of SVR, the tolerability and the adverse event profile of DAAs for the treatment of recurrent HCV infection after LT. Similarly, at the moment there are no indications about the potential predictors of SVR. It has to be underlined that in this particular setting, given the potential clinical benefits, the availability of clinical data on these new potent HCV inhibitors is urgently needed. For the moment there is no indication to their use in LT patients and the tolerability and the potential interaction with calcineurin inhibitors still represent a major drawback. Larger and well done clinical studies are urgently needed.

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