World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i13.3391

World J Gastroenterol 2014 April 7; 20(13): 3391-3400
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (2): Hepatitis C virus

Challenges of recurrent hepatitis C in the liver transplant patient

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Received: September 29, 2013 Revised: November 22, 2013
Accepted: March 7, 2014
Published online: April 7, 2014

Abstract

Cirrhosis secondary to hepatitis C virus (HCV) is a very common indication for liver transplant. Unfortunately recurrence of HCV is almost universal in patients who are viremic at the time of transplant. The progression of fibrosis has been shown to be more rapid in the post-transplant patients than in the transplant naïve, hence treatment of recurrent HCV needs to be considered for all patients with documented recurrent HCV. Management of recurrent HCV is a challenging situation both for patients and physicians due to multiple reasons as discussed in this review. The standard HCV treatment with pegylated interferon and Ribavarin can be considered in these patients but it leads to a lower rate of sustained virologic clearance than in the non-transplanted population. Some of the main challenges associated with treating recurrent HCV in post-transplant patients include the presence of cytopenias; need to monitor drug-drug interactions and the increased incidence of renal compromise. In spite of these obstacles all patients with recurrent HCV should be considered for treatment since it is associated with improvement in survival and a delay in fibrosis progression. With the arrival of direct acting antiviral drugs there is renewed hope for better outcomes in the treatment of post-transplant HCV recurrence. This review evaluates current literature on this topic and identifies challenges associated with the management of post-transplant HCV recurrence.

Key words: Cirrhosis; Hepatitis C; Recurrence; Transplant; Interferon

Core tip: Management of recurrent hepatitis C in post-transplant patient is challenging but can be rewarding as treatment has been shown to improve survival and slow fibrosis progression. This review summarizes major challenges in this population and discusses the natural history of post-transplant Hepatitis C virus (HCV), risk factors for HCV recurrence, management of immunosuppression and current treatment options. The preliminary data on use of newer direct acting antiviral drugs in the post-transplant setting has also been included.

Dhanasekaran R, Firpi RJ. Challenges of recurrent hepatitis C in the liver transplant patient. *World J Gastroenterol* 2014; 20(13): 3391-3400 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i13/3391.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i13.3391

INTRODUCTION

Cirrhosis related to hepatitis C virus (HCV) infection is a significant cause of morbidity and mortality worldwide. The World Health Organization estimates that around

150 million people worldwide are chronically infected with HCV, and that more than 350000 people die every year from HCV related liver diseases[1]. Liver transplantation (LT) is the best curative option for patients with HCV related cirrhosis and this is the leading indication for LT in the United States[2]. Unfortunately post-transplant HCV recurrence is almost universal, and it presents a challenging situation to both patients and transplant hepatologists alike. Patients who are wrestling post-transplant surgical complications, medication related side effects and rejection episodes have to also worry about ongoing allograft injury secondary to HCV recurrence. In addition, physicians face the challenge of identifying candidates eligible for antiviral therapy, ascertaining the ideal time to initiate therapy and find means to combat side effects of therapy, in this cohort of very sick patients.

NATURAL HISTORY OF RECURRENCE

Recurrence of HCV viremia occurs very early after transplant, with initial studies showing presence of HCV particles in serum of 96% of the patients who underwent LT for HCV[3]. Allograft infection is believed to occur during reperfusion of liver immediately after transplantation and in fact the viral particles have been found to replicate within few hours of transplantation[4]. HCV core and NS3 viral peptide sequences have been found to be identical before and after LT in most patients, suggesting that the sequence is largely preserved[5]. Also of concern is the fact that HCV infection is found to be more rapidly progressive in the post LT setting with two major forms being reported[6]. Severe cholestatic hepatitis is the more aggressive form and this presentation is unique to patients on immunosuppression who are exposed to very high viral load. The second form is the more common, chronic hepatitis with associated rapid progression of fibrosis.

As mentioned above, the recurrence of HCV viremia post LT is universal but the severity of recurrence and rate of fibrosis progression are variable and are influenced by multiple donor and recipient factors. And unfortunately liver tests are not sensitive or specific in identifying graft dysfunction or degree of fibrosis in post LT patients, which is the reason several centers propose performing annual protocol biopsies in patients transplanted for HCV. Early diagnosis of allograft injury can lead to earlier initiation of therapy, with the caveat that interpretation of liver biopsies is not straightforward in this population due to frequent overlapping pathologies like reperfusion injury or rejection episodes. These protocol biopsies have also been useful in understanding the natural history of recurrent HCV. Several studies have demonstrated accelerated rate of fibrosis progression leading to increased graft loss with reported rates of cirrhosis ranging from 20% to 54% at 5 years[7-10]. We routinely perform protocol biopsies in our center and early experience demonstrated accelerated rate of fibrosis in post LT patients at a rate of 0.8 per year and we found that the one year protocol biopsy was useful to predict rate of progression[11]. In a recent large multicenter study involving 1264 patients, the cumulative risk of cirrhosis at 3 years was 38% for women and 33% for men[12]. This rapid progression in fibrosis translates to overall worse clinical outcomes in HCV patients. In a retrospective analysis of UNOS database HCV recurrence was found to significantly and independently impair patient and allograft survival after liver transplantation[13]. In this large study involving more than 11000 patients, HCV was associated a 20% increased risk for mortality and 30% increased risk for graft failure.

RISK FACTORS FOR RECURRENCE

Donor factors

Several studies have found that HCV recurrence is more rapid and more severe in patients who received organs from older donors[14-16]. The reason for this is not entirely well understood, but it is probably multifactorial and is likely related to age related changes in liver including decreased hepatocyte volume, pseudocapillarization of sinusoids and reduced microcirculation[17,18]. Older livers also have changes in hepatic stellate cell activation and decreased liver regenerative capacity, which in the background of ongoing recurrence of hepatitis could contribute to the rapid progression of fibrosis in post-transplant patients[19]. Though donor age significantly affects outcome, it essentially is a non-modifiable risk factor. In this era of organ shortage, avoiding older age donors for hepatitis C patients is not a practical solution since more than a third of adult deceased donors are older than fifty years[2].

A few early studies had suggested than recipients of living donor liver transplantation (LDLT) were at higher risk for recurrence than deceased donor transplants (DDLT)[20]. Garcia-Retortillo *et al*[20] reported that LDLT patients had a 2.8-fold higher risk of developing severe recurrence when compared to DDLT. But other well designed larger studies have refuted these results[21-23]. And one of the studies with long term follow up actually showed better outcomes in LDLT with improved survival and lower fibrosis scores[24]. In a recent meta-analysis of fourteen studies, with a total of 2024 participants, no significant differences were found between LDLT and DDLT in terms of long-term patient survival, graft survival, or HCV recurrence. In summary, LDLT can be safely offered in experienced centers to HCV patients, without impacting significantly outcomes.

Other donor related factors that have been studied include HLA matching, degree of steatosis of donor liver, occurrence of reperfusion injury and cold ischemic time. But none of these factors have been established as playing a causative role in fibrosis progression. Donor livers with > 40%-50% steatosis are usually not accepted by transplant centers since these livers have been associated with higher rates of primary non function and graft failure[25,26]. Also, presence of significant donor steatosis

has also been associated with more rapid progression of HCV recurrence; raising the question of whether such livers should even be used in this subset. But data on milder degree of steatosis is not clear or uniform. A few studies have proposed that it is safe to use donor livers with mild steatosis, as they do not have any impact on graft survival[27,28]. But Briceño *et al*[29] reported that three year post LT graft survival was 95%, if steatosis was < 30% and 69% if donor steatosis was > 30% ($P = 0.0001$). This study goes so far as to suggest that LT with > 30% steatotic donor livers should be precluded for HCV recipients. This appears to be safe approach, but we know that 20%-25% of the general population has hepatic steatosis secondary to nonalcoholic fatty liver disease. And the people in the donor pool, which includes people involved in motor vehicle accidents, usually have a history of alcohol use related steatosis too. From a practical standpoint it might not be entirely possible to direct all livers with greater than 30% steatosis away from hepatitis C patients, but recognition of risk for rapid progression of HCV recurrence can lead to closer follow up and earlier treatment initiation.

Viral factors

Viral replication can be detected very early in the post-operative period[30] but viral kinetics are variable. Serum HCV RNA levels typically increase rapidly from the second week post LT and peak by the fourth postoperative month[31]. Outside of the transplant setting, the level of viremia has not been shown to correlate with disease severity in patients with HCV[32,33]. However, it appears to play a significant role in progression of post LT recurrence. A few early studies did not show correlation between level of viremia and risk for progression and even suggested that a carrier state might exist with high levels of viremia and absent inflammation[8,34]. Several other well conducted studies have shown that high level of post LT viremia was independently associated with more rapid progression of hepatitis[7,35-37]. Shackel *et al*[36] reported that a one year peak viral load > 10^7 IU/mL was associated with a hazard ratio of 8.68 for worse patient survival. An international consensus panel has indeed accepted both pre and early post LT viral load as established risk factors for severe recurrence[38]. A correlation between early levels of viremia and subsequent allograft injury suggests that initiation of antiviral therapy early in the post LT course might be desirable. Another viral factor that has been explored is genotype, with early studies suggesting than genotype1b was associated with higher risk for recurrent hepatitis[26,39]. But later studies did not find any influence of genotype on outcomes[39,40].

Polymorphism in IL28B gene, which encodes interferon-lambda-3 (IFN-λ-3), has been established as a predictor of response to IFN based therapy in the non-transplant setting[41]. Charlton *et al*[42] examined the impact of IL28B polymorphisms in the post LT setting and evaluated the role of both donor and recipient IL28B status. Both recipient and donor liver IL28B genotype were strongly and independently associated with IFN-based treatment response in patients after LT. And interestingly recipient IL28B TT genotype was associated with more severe histological recurrence of HCV. In contrast, Lange *et al*[43] showed that donor IL28B had significant impact on the natural course and treatment outcome of HCV liver graft reinfection. Our center published data found that the rate of sustained viral response (SVR) to HCV therapy was 100% if both recipient and donor were CC genotype, while the SVR was only 25% if neither donor nor recipient had a CC genotype. Recipients and donors with CC genotype also had less fibrosis than recipients with genotypes CT and TT[44]. Overall, IL28B genotype appears to affect both the treatment response and also the natural history of recurrence. Consequently, once the relationships are more clearly established, there might be a role for preferentially offering donor livers with CC genotype to HCV patients.

IMMUNOSUPPRESSION

Corticosteroids

Corticosteroids are used routinely as part of immunosuppressive regimen in LT patients both for induction and for management of episodes of acute cellular rejection (ACR). Initial studies in the non-transplant setting showed that use of steroids lead to a dose dependent increase in HCV viral load[45]. Gane *et al*[7] studied viral replication in post LT patients receiving steroids and showed that a more dramatic increase in viral load occurred in this population and methylprednisolone treatment for ACR was found to lead to a 4-100 fold increase in serum HCV RNA. The mechanism for this is not clearly understood, but in vitro studies using a replicon model showed that treatment of hepatocytes with clinically relevant concentrations of steroids actually resulted in a slight decrease in HCV replication[46]. Therefore, the rapid replication noted *in vivo* is probably more related to the suppressed host immune response than to the virus. Steroids have been shown to mediate suppression of virus-specific plasmacytoid dendritic cells and T-cell responses potentially leading to unchecked viral replication[47,48]. Keeping in line with these findings, Berenguer *et al*[49] demonstrated that avoiding rapid steroid tapering and using a steroid sparing double induction immunosuppression regimen led to less severe disease. And other studies have similarly suggested that slow tapering of steroids and use of lower doses lead to better outcomes in HCV patients[50]. The results from clinical observational studies mentioned above appeared to support the idea of avoiding steroid boluses and avoid high dose steroids for induction, but the results from randomized controlled trials have been mixed.

A recently published randomized controlled trial divided 75 HCV positive recipients to receive tacrolimus (TAC) plus a corticosteroid or TAC plus mycophenolate mofetil. They found that the steroid-avoidance regimen had no apparent impact on LDLT outcomes like survival

or fibrosis progression[51]. But steroid boluses were used for episodes of acute cellular rejection in both arms of the study. In another two year prospective randomized study, steroid free immunosuppression was compared to steroid use and they found that steroid avoidance with basiliximab, calcineurin inhibitor, and mycophenolate sodium was safe and as effective as steroid containing immunosuppression in adult OLT[52]. Overall there appeared to be no benefit to the steroid free protocol in terms of ACR, fibrosis progression, patient survival, or graft survival rates[53]. In summary, steroids should be used cautiously in post LT HCV patients and, when needed, lower doses should be used with a slow taper. But there is not enough evidence to switch all HCV patients to a completely steroid free immunosuppression regimen.

Calcineurin inhibitors

TAC and Cyclosporine A (CysA) are the most widely used maintenance immunosuppression in post LT patients. In vitro studies have shown that CysA has a suppressive effect on the HCV replication and protein expression in cultured human hepatocyte cells and this effect appears to be independent of its immunosuppressive function[54,55]. We found similar effects in-vivo in two clinical trials at our center where the use of CysA was found to be associated with a modest HCV RNA drop and appeared to enhance the antiviral response to interferon based antiviral therapy when compared to TAC[56,57]. Similarly a meta-analysis of 17 studies concluded that CysA was associated with a marginally higher relative risk (RR) for achieving SVR with antiviral therapy when compared to TAC[58]. Though the data on antiviral effects of CysA are convincing, the same is not true regarding clinical outcome parameters like survival or rejection rates. A meta-analysis of 16 randomized trials including patients transplanted for all etiologies concluded that TAC was superior to CysA in improving survival and preventing acute rejection[59]. There is a lack of large randomized controlled trials addressing this question specifically in HCV patients. A retrospective study concluded that in patients undergoing LT for HCV-related liver disease, post-transplantation outcome was not related to the Calcineurin Inhibitors used, with no differences in bridging fibrosis, cirrhosis, cholestatic hepatitis, allograft loss or mortality between TAC and CysA[60]. In another retrospective analysis of data from UNOS database suggested that using CysA was associated with increased risk of patient death and graft failure[61]. Adding to the complexity of the situation, recent data has shown that the use of TAC is associated with ACR in patients with certain IL-28B polymorphism and CysA might be beneficial in this specific subset[62].

Data on the role of other maintenance immunosuppressants like Azathioprine and Rapamycin in HCV recurrence or fibrosis progression is not very clear. Samonakis *et al*[63] have suggested that there may be a beneficial effect of maintenance azathioprine given for 6 mo or longer based on observational studies. Mycophenolic acid (MPA) has also been shown to be an inhibitor of HCV replication[64,65]. MPA was shown to have a distinct anti-HCV mechanism of action, independent of cell proliferation and guanosine depletion. Further clinical studies are needed exploring its use in HCV patients. Anti-lymphocyte agents which are used to treat rejection are associated with worse recurrence and hence have to be employed with caution[63].

TREATMENT

Preemptive therapy

Treating HCV patients on liver transplant waiting list can be considered as a prophylactic approach since absence of viremia at the time of transplant can prevent recurrence. Unfortunately, tolerance for treatment is very low in these patients with decompensated liver disease[66]. When newer drugs for HCV are available in the future there is hope that higher proportion of patients on the LT waiting list will be virus negative. Another treatment strategy is termed pre-emptive therapy, where patients are initiated on antiviral therapy early in the post LT period before the recurrence of viremia. The rationale behind this strategy is to prevent liver inflammation or fibrosis by early suppression of the virus. Although the reasoning behind this hypothesis is sound, data from clinical observational studies and trials do not support this strategy. High rates of discontinuation due to side effects and poor SVR rates plague this approach. In one of the earlier studies addressing this question Mazzaferro *et al*[67] initiated antiviral therapy at a median duration of 18 d post LT and demonstrated SVR rate of 33% with milder graft injury both in patients who remained HCV negative and in patients who turned HCV positive despite therapy and similar results were demonstrated in patients who received a living donor liver transplant[68]. These results have not been consistently reproduced. In a small randomized controlled trial by Singh *et al*[69] pre-emptive treatment delayed the occurrence of HCV hepatitis, but did not decrease the incidence or the severity of HCV hepatitis and this delay has been demonstrated in studies with long term follow-up too[70]. Unfortunately many studies have shown that both eligibility for therapy and tolerability for these medications are low in this post LT cohort. In Shergill *et al*[70] randomized trial only 41% of the post LT patients were eligible to receive pre-emptive antiviral therapy and dose reductions and discontinuations were required in 85% and 37% of patients, respectively. Other studies have shown similar side effect profile and low SVR rates[71]. In the immediate post LT period, most patients are battling renal dysfunction, cytopenias, immunosuppression related side effects and episodes of acute rejection which is probably why the physiologic reserve to endure side effects from PEG IFN or Ribavarin is low. So until safer and more effective antiviral drugs are available the pre-emptive strategy cannot be recommended for routine practice.

Table 1 Clinical outcome of treatment for post-transplant hepatitis C recurrence

Ref.	I	Study design	SVR	Fibrosis progression	Discontinuance
Roche *et al*[85] (2008)	113	Retrospective study	38%	Fibrosis stage remained stable (78.5%) in patients with SVR and increased (44%) in non-responders	24% overall did not complete therapy. 38% required the premature discontinuation of either IFN, RBV, or both agents
Carrión *et al*[81] (2007)	81	Randomized controlled trial	48% in early fibrosis and 18% in advanced fibrosis	Fibrosis progression -26% in treated group *vs* 70% in untreated group	Treatment interruption in 22% and 56% of patients with mild and advanced fibrosis respectively
Neff *et al*[86] (2004)	57	Retrospective study	24.5% virus negative at 48 wk	Responders to therapy trended toward improvement in level of fibrosis	Overall discontinuation rate 31.5%. Dose adjustments in 74%
Oton *et al*[87] (2006)	55	Prospective cohort study	43.60%	No improvement in fibrosis progression	29% discontinued due to intolerance
Samuel *et al*[83] (2003)	52	Randomized controlled trial	21%	No impact on fibrosis progression	Treatment interruption 43%
Fernández *et al*[82] (2006)	47	Prospective cohort study	23%	Significant histological improvement in 23%	Treatment interruption in 21%
Mukherjee *et al*[84] (2006)	39	Prospective cohort study	33.30%	Improved or stable fibrosis scores were also demonstrated in 66.7% of non-responder	43.6% discontinuation rates

SVR: Sustained virologic response; IFN: Interferon; RBV: Ribavarin.

Treatment of established recurrence

Most centers initiate treatment of HCV after histological recurrence has been documented on liver biopsy. The AALSD guidelines on HCV therapy also recommend treatment initiation in appropriate candidates after demonstration of recurrent histologic disease, but the stage of fibrosis at which therapy should optimally be started is not clear ant it does vary between centers. Results from initial studies evaluating efficacy of IFN monotherapy were disappointing[72]. But subsequent studies with dual therapy of IFN and Ribavarin, more specifically with pegylated IFN (PEG IFN) have been encouraging[73]. In a systematic review by Berenguer *et al*[74] of 19 studies including 611 patients who received PEG-IFN alfa with ribavirin for established histologic recurrence of HCV, the mean SVR rate was found to be 30.2% despite high rate of treatment discontinuation and dose reductions due to adverse events. Therapy has also been found to be cost effective in a study by Logge *et al*[75] where they used a Markov model for disease progression. Several studies have looked at prognostic factors for achievement of SVR and have demonstrated an association with lower pretreatment HCV RNA, HCV genotype 2 or 3, adherence to therapy, and achievement of an early virological response[76,77].

Clinically, the most important question is whether treatment is associated with improvement in clinical outcomes like survival or fibrosis progression. Selzner *et al*[78] retrospectively analyzed long term outcome of 446 patients treated with dual therapy found that treatment was independently associated with significantly prolonged survival. Similar encouraging survival outcome has also been demonstrated in few other studies[79,80]. Another important clinical outcome is rate of fibrosis progression and data on the effect of treatment on fibrosis progression has not been uniform (Table 1)[81-87]. In one of the early observational studies analyzing histological response from our center, we demonstrated that fibrosis progression was slower in patients who underwent HCV therapy in a cohort of 34 patients[88]. Selzner *et al*[78] also reported improved histologic outcome with PEG IFN based treatment for HCV recurrence but paired biopsies were available only in 52% of this study group. Results from a few other smaller studies also suggest that treatment leads to improvement in fibrosis but there has been variability in how fibrosis data is reported[89,90]. This probably is the reason that a meta-analysis of 14 studies which analyzed histologic response by Berenguer *et al*[74] found a significant heterogeneity among studies and only a minority of patients underwent liver biopsy both prior to and after antiviral therapy. Despite these limitations it did appear that achieving SVR led to improvement in the stage of fibrosis and the necroinflammatory grade, while non-responders generally experienced progressive fibrosis.

The face of HCV therapy is rapidly changing with the arrival of newer, more potent antiviral drugs. Direct acting antiviral drugs like Boceprevir and Telaprevir were approved in 2011 for treatment of HCV and they have shown significant increase in SVR when used in combination with PEG IFN and Ribavarin. In phase Ⅲ trials in the non-transplant setting 63%-75% of treatment naïve patients receiving triple therapy achieved SVR[91,92]. But triple therapy does come with its own set of challenges which are more conspicuous in the transplant setting including drug interactions, need for frequent dosing, increased incidence of cytopenias, high costs with proven efficacy only in HCV genotype 1 patients. Telaprevir is an inhibitor of the enzyme cytochrome P450 3A which is involved in the metabolism of both CysA and TAC. Garg *et al*[93] conducted a phase I study to assess the interaction between Telaprevir and CysA or TAC. And they showed that Telaprevir increased CysA exposure by approximately 4.6-fold and increased TAC exposure by approximately 70-fold. In a pilot study to assess the safety and efficacy of triple therapy in LT patients, data were gathered for 12 wk in nine HCV patients who were treated with a combi-

nation of Telaprevir, PEG IFN, and ribavirin along with TAC, CysA or Sirolimus[94]. It was found that drug-drug interactions between TVR and immunosuppressants could be managed with close monitoring of trough levels and adequate dosage adjustments. A recent cohort study of patients treated with Boceprevir (n = 18) or Telaprevir (n = 19) based triple therapy demonstrated that SVR rates were comparable to dual therapy but around a third of patients developed severe anemia requiring transfusion[95]. Results from ongoing trials involving triple therapy in this special population are expected in the near future. The potential for newer drugs which can potentially be used in regimens without IFN and Ribavarin will change the treatment scenario drastically. A case report of a patient with severe recurrent HCV who was treated with Sofosbuvir, an HCV polymerase inhibitor, and Daclatasvir, an HCV NS5A replication complex inhibitor for 24 wk demonstrated undetectable HCV RNA within 4 wk of initiating treatment, and the patient achieved SVR at 9 mo[96]. If these promising results hold good in clinical trials, several of the challenges associated with post-transplant hepatitis C recurrence could be tackled more effectively.

CONCLUSION

Recurrence of HCV presents a clinically challenging situation in post-transplant patients. The recurrence of viremia is universal and the progression of fibrosis is rapid. Incidence of cirrhosis and graft failure is significantly higher in untreated patients translating to poor overall clinical outcome. Multiple donor, viral and immunosuppression related factors have been found to influence rate of fibrosis progression and clinical outcome. Treatment of recurrence with PEG IFN and Ribavarin is efficacious in this population albeit with lower SVR rates and worse side effect profile. Therapy is associated with multiple challenges including severe cytopenias, drug interactions and renal failure. But given the improvement in survival and fibrosis progression associated with treatment, physicians should try to treat all eligible patients with recurrence, despite obstacles. Direct acting antiviral drugs have ushered a new era in the management of HCV patients. Emerging data on direct acting antivirals in the post-transplant setting shows promise in terms of safety and efficacy with appropriate monitoring and dose adjustment of immunosuppressants. Though multiple studies have investigated the role of antiviral therapy, well designed randomized controlled trials further exploring various aspects of HCV therapy in post LT population are urgently needed.

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ISSN 1007-9327
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