Review Article

Management of Hepatitis C Before and After Liver Transplantation in the Era of Rapidly Evolving Therapeutic Advances

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Abstract

Management of hepatitis C (HCV) in liver transplantation (LT) population presents unique challenges. Suboptimal graft survival in HCV+ LT recipients is attributable to universal HCV recurrence following LT. Although eradication of HCV prior to LT is ideal for the prevention of HCV recurrence it is often limited by adverse events, particularly in patients with advanced cirrhosis. Antiviral therapy in LT candidates needs careful monitoring, and prophylaxis with HCV antibodies is ineffective. Early antiviral therapy after LT has been investigated, but no clear benefit has been demonstrated. Protocol liver biopsy is generally recommended in HCV+ LT recipients, and antiviral therapy can be considered in those with severe/progressive HCV recurrence. Sustained virological response (SVR) can be achieved in approximately 30% of LT recipients with pegylated interferon/ribavirin (PEG-IFN/RBV) with survival benefit, but adverse effects are common. Favorable patient characteristics for response to therapy include non-1 genotype, previously untreated, low baseline HCV-RNA, and donor IL28B genotype CC. Direct acting antiviral (DAA)-based triple therapy is associated with higher rates of SVR, but with similar or slightly higher rates of side effects, and immunosuppressive regimens need to be closely monitored and adjusted during the treatment period. Notably, the safety and efficacy of HCV treatment are very likely to improve with newer generation DAA. The benefit of immunosuppressive strategy on the natural history HCV recurrence has not been well elucidated. Based upon available evidence, cyclosporine A (CSA), mycophenolate mofetil (MMF), and sirolimus appear to have a neutral or small beneficial impact on HCV recurrence. Donor interleukin 28 B (IL28B) polymorphisms appear to impact the course and treatment outcomes in recurrent HCV. Retransplantation should be considered for patients with reasonable survival probability.

Introduction

Chronic hepatitis C virus (HCV) infection is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide. As a consequence, it is the most common indication for liver transplantation (LT) in the United States, Japan, and many countries in Europe. Despite advances in anti-viral therapy, current estimates indicate that the prevalence of HCV and its associated complications will continue to rise over the next two decades.[1,2] Recurrence of HCV in the allograft is universal, occurring soon after liver transplantation, and may be associated with accelerated progression to cirrhosis, graft loss, and death.[2,3] Therefore, management of chronic HCV infection before and after LT is an important component of current and future clinical practice.

Current approaches to the management of HCV patients before and after LT fall into four broad categories based on the time of intervention: (1) treatment of patients with cirrhosis awaiting LT; (2) prophylaxis defined as initiation of therapy at the time of LT and continued post-LT with the goal of preventing recurrent infection; (3) early post-LT (within the first 6 months after LT); and (4) HCV therapy for established disease.[4]

The overall outcome of antiviral therapy in this setting is suboptimal; however, it can be successfully utilized in selected populations with careful monitoring. Unique challenges and issues in the LT population in the context of HCV therapy include the tolerability of pegylated-interferon (PEG-IFN) and ribavirin (RBV) and more recently of the direct acting antivirals (DAA), the need to modify immunosuppressive regimens during DAA therapy because of drug-drug interactions, the risk of graft rejection, and the role of genetic polymorphisms on response to therapy.[5]

Natural history of hepatitis C before and after LT

Approximately 15–20% of patients with HCV-related cirrhosis evolve to hepatic decompensation and/or develop HCC within 10 years.[6] If these complications are left untreated,

prognosis is poor and these patients will require LT as a life-saving procedure. In addition, graft and patient survival are significantly reduced in HCV-positive recipients compared to HCV-negative recipients, a difference mainly accounted for by recurrence of HCV infection in the graft.[7] HCV recurrence is almost universal and its severity depends on several host, viral, donor, and transplant factors (Table 1).[2,8–10]

Following LT, the liver graft is re-infected upon reperfusion, and is accompanied by a rise in HCV viral load that peaks around 3–4 months. Most patients develop features of acute hepatitis between 4 and 12 weeks after LT.[4] Though serum transaminases and HCV-RNA generally settle down to normal or near normal range, spontaneous viral clearance has not been observed.[2–4] At the end of the first year, HCV-RNA levels are, on an average, 10-20-fold higher than pre-LT levels. Histological evidence of chronic hepatitis C is encountered in 50–80% of patients after 6–12 months.[2,3,11] The natural course of hepatitis C is accelerated in liver transplant recipients, with more than 40% progressing to cirrhosis

Table 1. Factors associated with an increased incidence and/or increased severity of recurrence in HCV following liver transplantation

Risk factors for severe HCV recurrence

Pre-transplant factors

Host factors

- Advanced age (>50 years)
- Reduced immune responses (T-cells, natural killer cells)
- Non-CC *IL28B* genotypes
- Cryoglobulinemia*

Viral factors

- Genotype 1
- High HCV-RNA levels
- HIV co-infection

Donor factors

- Advanced donor age (>35 years)
- Liver steatosis
- Non-CC *IL28B* genotypes
- HLA mismatch*
- High liver iron concentration*

Transplant factors

- Prolonged cold ischemic time (>12 hours)
- Preservative injury

Post-transplant factors

- Early / high HCV-RNA levels
- Rejection episode(s)
- Corticosteroids: pulse therapy, high accumulation dose, early/ rapid withdrawal
- CMV and HHV-6* infection
- OKT3, ALG*, ATG*
- Post-LT diabetes mellitus*

*Possible risk factor (limited and/or controversial data)
Abbreviations: HCV, hepatitis C virus; LT, liver transplantation; HIV, human immunodeficiency virus; HLA, human leukocyte antigen CMV, cytomegalovirus; HHV, human herpes virus; ALG, anti-lymphocyte globulins; ATG, anti-thymocyte globulins

within 10 years and approximately 50% developing liver failure shortly thereafter (Fig. 1).[2–6,11]

A subset of patients (2–9%) may develop post-LT cholestatic hepatitis C, which is characterized by persistent cholestasis of at least 4 weeks in duration, high HCV-RNA, hepatocyte ballooning, rapid progression to graft failure, and, in the absence of biliary and hepatic artery complications, sepsis and drug-related cholestasis.[12] This complication is usually resistant to antiviral therapy and leads to death in more than 50% of patients within the first year after LT; retransplantation (RT) is associated with poor outcomes.[2,12,13]

Due to the lack of sensitivity and specificity of serum transaminases in determining the severity of recurrent hepatitis, HCV recipients ideally should undergo protocol liver biopsies in order to determine disease severity and prognosis starting from around 6–12 months and then annually following LT. Early post-LT histology has been consistently predictive of subsequent fibrosis progression.[2,3] Several preliminary studies have suggested that non-invasive markers, especially transient elastography, correlated well with the degree of graft fibrosis and outcomes in HCV+ LT recipients.[14–17] A recent study of 144 HCV-infected and 48 non-HCV-infected LT recipients reported that the liver stiffness measurement at one year after LT is a valuable predictor of liver-related outcomes in recurrent HCV (cumulative probabilities of liver decompensation five years after LT were 8% for patients with liver stiffness measurement <8.7 kilopascals versus 47% for patients with $\geqslant$ 8.7 kilopascals; $p < 0.001$) and can be used in clinical practice to identify the best candidates for antiviral therapy.[18] This tool can be very useful as an alternative or complementary test to invasive protocol biopsies for monitoring post-LT recurrent hepatitis C and to identify the best candidates for antiviral therapy. However, studies with a longer follow-up period and larger sample size are needed to confirm these preliminary results. Nevertheless, the decision to intervene therapeutically has varied across centers and is mostly tailored to the severity of liver disease, although a strategy to treat all with any degree of recurrent hepatitis has also been pursued.

Management of hepatitis C before and after LT

The goal of HCV management in the setting of LT is to prevent or cure recurrent HCV disease. Current approaches can be divided into four broad categories according to the time of intervention (Fig. 2).[4]

Management of hepatitis C in LT candidates

Management of patients with HCV cirrhosis awaiting LT aims to attain sustained virological response (SVR), slow liver disease progression, and prevention of liver graft infection. Successful viral eradication in patients with cirrhosis independently reduces the likelihood of clinical decompensation and improves survival, which may then facilitate, delay, or, in a small proportion of patients, avoid LT.[4,19] Furthermore, high pre-LT HCV-RNA levels are strongly associated with poor graft and patient survival and are driven by HCV recurrence. Taken together, these findings support the necessity to treat HCV prior to LT. Notably, in patients who achieved SVR prior to LT, the incidence of HCV recurrence is very low (0–20%).[2–4,9,19]

Several uncontrolled and controlled prospective studies have evaluated the efficacy and safety of antiviral therapy
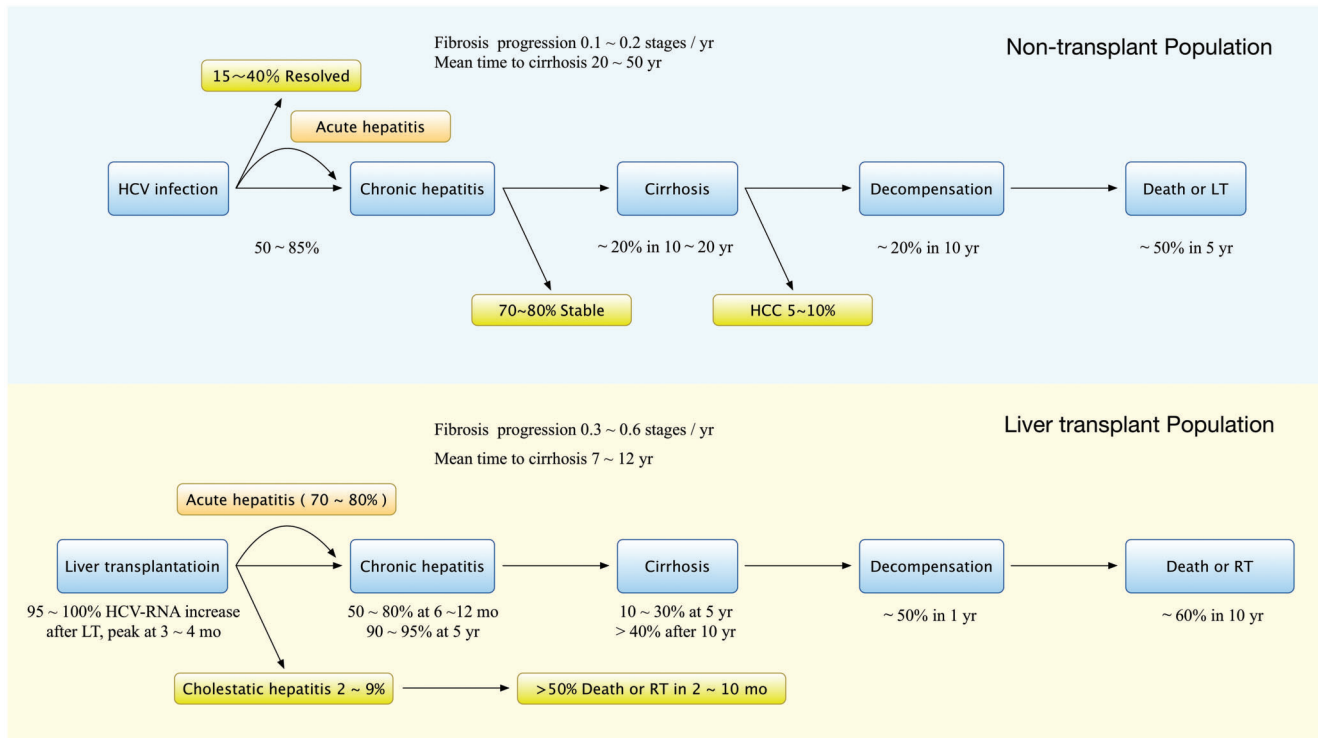
Fig. 1. Natural history of HCV in non-transplant and liver transplant populations. Abbreviations: HCV, hepatitis C virus; LT, liver transplantation; RT, retransplantation

with IFN or PEG-IFN and RBV in LT candidates. SVR was achieved in 7–30% of patients with HCV genotype 1, whereas 44–57% of patients with genotype 2/3 achieved SVR.[4,20] Predictors of SVR were genotypes 2/3, early virological response (EVR), low HCV-RNA, adherence to full dose(s)/ duration of treatment, and *IL28B* genotype CC.[21] Everson *et al.* treated 124 patients with decompensated cirrhosis by a low accelerating dosage regimen (LADR) using either IFN 1.5 MU thrice weekly or PEG-IFN alfa-2b 0.5 μg/kg once weekly plus RBV 600 mg/day, and gradually increased the doses every two weeks until they reached the maximum tolerated or target standard doses. SVR was 13% in patients with genotype 1 and 50% in those patients with non-1 genotypes. Adverse events were frequent in patients with cirrhosis awaiting LT, which led to dose reduction in 40–70% and treatment discontinuation in 13–40% of patients.[4] The incidence of infections, particularly spontaneous bacterial peritonitis in patients not receiving quinolone prophylaxis, was significantly higher in patients on antiviral therapy than in those who did not receive therapy.[22] Treatment-induced cytopenias have commonly been managed by dose reduction and hematopoietic growth factors.

Currently, four direct-acting antivirals, including boceprevir (BOC), telaprevir (TVR), simeprevir, and sofosbuvir, have been approved for the treatment of HCV genotype 1 as part of a three-drug combination with PEG-IFN/RBV. These DAA-based triple therapies have been shown to improve virological outcomes in HCV genotype 1 patients, with an SVR of up to 65–86% in treatment naïve patients and 29–83% in previous relapsers/non-responders.[23–28] However, the data on safety

and efficacy of DAA-based triple therapy in cirrhosis and LT candidates are limited. Adverse effects of treatment, particularly anemia, are more frequently observed with BOC and TVR therapies.[24–27] Though treatment-induced anemia is generally manageable by dose reduction and erythropoiesis-stimulating agent, severe anemia could develop more frequently and lead to treatment discontinuation in more vulnerable cirrhotic patients. Cure rates in patients with advanced fibrosis were significantly lower than in patients with mild to moderate fibrosis, although results were still encouraging.[20] However, there is no data available regarding the efficacy of BOC and TVR in patients with decompensated cirrhosis, where safety is the major concern.[20] A French Cohort (CUPIC Study Group) of compensated HCV cirrhosis treated with BOC or TVR (N=674) reported a high incidence of serious adverse events (40%), severe complications, death (6%), and a difficult management of anemia (63%).[29] Death or severe complications were related to platelets count $\leqslant$100,000/mm^3 (OR 3.11, 95% CI; 1.30–7.41) and albumin <3.5 g/L (OR 6.33, 95%CI; 2.66–15.07), with a risk of 44% in patients with both.[29]

In the foreseeable future, IFN-free DAA regimens are likely to become available and expected to have high efficacy with low side effects,[30] which are perhaps worthy options for managing HCV in LT candidates. There was a recent case report using all-oral DAA (initially TVR and RBV and then BOC and RBV) in the pre-transplant period, to prevent reinfection of the liver graft after LT for advanced HCV-related cirrhosis.[31] A preliminarily report of the multi-center, open-label Phase 2 Study (N=61) evaluating sofosbuvir plus RBV (taken

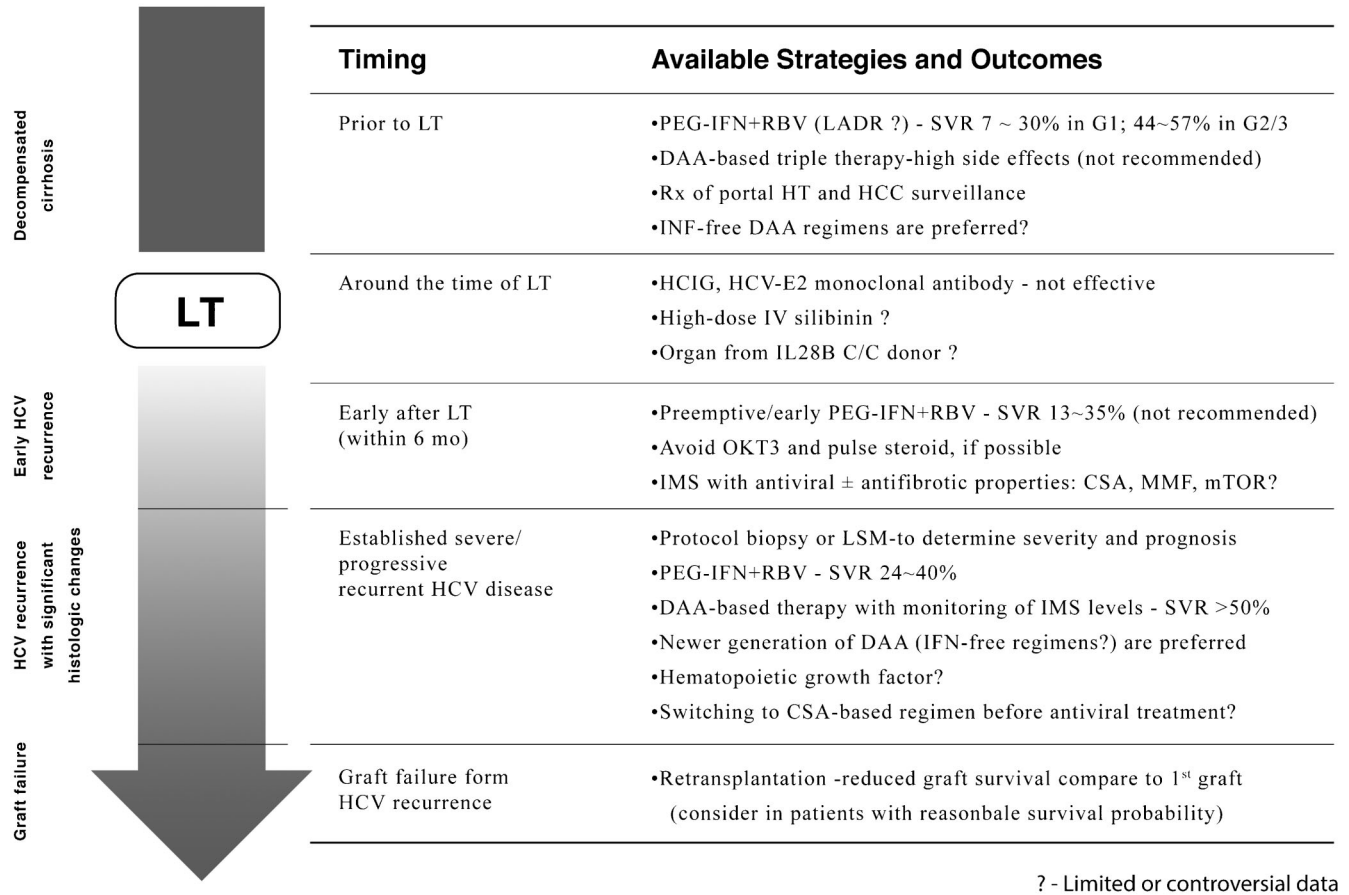|	Timing	Available Strategies and Outcomes
Decompensated cirrhosis	Prior to LT	•PEG-IFN+RBV (LADR ?) - SVR 7 ~ 30% in G1; 44~57% in G2/3 •DAA-based triple therapy-high side effects (not recommended) •Rx of portal HT and HCC surveillance •INF-free DAA regimens are preferred?
LT	Around the time of LT	•HCIG, HCV-E2 monoclonal antibody - not effective •High-dose IV silibinin ? •Organ from IL28B C/C donor ?
Early HCV recurrence	Early after LT (within 6 mo)	•Preemptive/early PEG-IFN+RBV - SVR 13~35% (not recommended) •Avoid OKT3 and pulse steroid, if possible •IMS with antiviral ± antifibrotic properties: CSA, MMF, mTOR?
HCV recurrence with significant histologic changes	Established severe/ progressive recurrent HCV disease	•Protocol biopsy or LSM-to determine severity and prognosis •PEG-IFN+RBV - SVR 24~40% •DAA-based therapy with monitoring of IMS levels - SVR >50% •Newer generation of DAA (IFN-free regimens?) are preferred •Hematopoietic growth factor? •Switching to CSA-based regimen before antiviral treatment?
Graft failure	Graft failure form HCV recurrence	•Retransplantation -reduced graft survival compare to 1st graft (consider in patients with reasonbale survival probability)

? - Limited or controversial data

Fig. 2. Summary of available HCV management options before and after liver transplantation. Abbreviations: HCV, hepatitis C virus; LT, liver transplantation; PEG-IFN, pegylated interferon; RBV, ribavirin, LADR, low accelerated dose regimen; SVR, sustained virologic response; G, genotype; HCC, hepatocellular carcinoma; IFN, interferon; DAA, direct acting antivirals; HCIG, Hepatitis C immune globulin; IV, intravenous; IL, interleukin; IMS, immunosuppressive drugs; CSA, cyclosporine A; MMF, mycophenolate mofetil; mTOR, the mammalian target of rapamycin inhibitors; LSM, liver stiffness measurement

for 24–48 weeks before LT) to prevent HCV recurrence following LT has shown promising results.[32] Participants had well-compensated liver disease (the median MELD score was 8) and were listed for LT due to HCC; 73% had HCV genotype 1, 13% had genotype 2, 12% had genotype 3, and 2% had genotype 4. More than 90% of patients who received treatment had undetectable HCV-RNA at the time of LT. Among those with undetectable HCV at LT, 64% maintained viral suppression at 12 weeks post-LT.[32] Sofosbuvir/RBV was generally safe and well-tolerated with 11 serious adverse events reported during the study (none of which were considered related to sofosbuvir).[32]

Taken together, antiviral therapy with PEG-IFN/RBV in the setting of HCV cirrhosis should be used in properly selected populations with careful monitoring by those experienced in hepatitis C treatment. Given the high rate of serious adverse events among patients with more advanced liver disease, treatment is contraindicated when the Child-Turcotte-Pugh (CTP) score is >11 or the Model of End-stage Liver Disease (MELD) score is >25, whereas treatment should be considered if CTP ≤7 or MELD ≤18.[3,33] DAA-based triple therapy should not be used in LT candidates outside of carefully designed clinical trials, and IFN-free regimens are required for this vulnerable population.

Prophylactic therapy

Immune globulin containing virus-specific antibodies have been shown to be effective in the treatment of several viral diseases, as well as in the prevention of recurrent hepatitis B after LT.[4] In animal studies, immune globulin enriched in antibody to HCV (HCIG) was able to neutralize infectious inoculates and delay or prevent HCV infection.[34] Therefore, HCIG might have a role in preventing recurrent HCV after LT.

Unfortunately, clinical studies of HCV antibody therapy using polyclonal HCIG[34] and anti-E2 monoclonal antibody[35] have not proven to be effective. In a Phase II study of monoclonal antibody HCV-Ab^{XTL}68, 24 patients were randomized to receive 2–4 infusions of either placebo, low-dose HCV-Ab^{XTL}68, or high-dose HCV-Ab^{XTL}68 during the first 24 hours after LT, followed by daily infusions for six days, weekly infusions for three weeks, and either two or four weekly infusions for eight weeks. Significant HCV-RNA reduction was achieved in a dose-related manner, although all patients became viremic after LT.[35] Preliminary data suggested that high-dose intravenous silibinin given immediately after LT may prevent HCV recurrence.[36] However, this approach needs to be further evaluated. Recently, a Cochrane Systematic Review (included 10 trials; 441 HCV+ LT recipients) reported that there

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were no significant differences in mortality rates, worsening of fibrosis, HCV recurrence, serious adverse events, or graft rejection between intervention and control groups.[37] Therefore, at present, there is no demonstrated role for antiviral or HCV antibody therapy in the management of HCV patients undergoing LT.

Early post-transplant or preemptive antiviral therapy

Preemptive antiviral strategy typically initiates antiviral treatment within the first two months after LT. The rationale for this approach is supported by the experience from the treatment of acute hepatitis C in the non-transplant population, where SVR rates are very high when therapy is initiated early.[4] Therefore, intervening at an early time point with relatively low HCV-RNA levels in the absence of significant histological changes in the graft might lead to better treatment outcomes in recurrence HCV infection. The majority of clinical studies of preemptive therapy in LT recipients was uncontrolled and used a combination of conventional IFN/RBV.[4,20] Overall results have been somewhat disappointing; rates of SVR varied between 5–33% in genotype 1 and 14–100% in genotype 2/3 patients.[4,20] More recent controlled studies have evaluated the efficacy of 48-week therapy in the early post-LT (mean 3–4 months) with standard dose[38] and escalating dose regimen of PEG-IFN/RBV;[39] SVR was achieved in 13–35% of patients.[4,38,39] Preemptive treatment was associated with high rates of treatment dose reduction (28–85%) and discontinuation (0–37%). Furthermore, transplant-related factors, such as high levels of immunosuppression, can decrease the likelihood of HCV eradication, and post-surgical and infectious complications may preclude patients as treatment candidates.

A recent multi-center, randomized controlled trial of 115 patients comparing early treatment (10–26 weeks after LT) and treatment of established histologic HCV recurrence (Phoenix trial) with PEG-IFN/RBV showed similar SVR rates in both treatment groups (22% vs. 21%, respectively). Survival, adverse events, dose reduction, and acute cellular rejection (ACR) rates were no different between the groups.[40] Thus it appears that there is no established role of early post-LT HCV therapy.

Treatment of established HCV recurrence

Antiviral therapy is considered in LT recipients who develop significant or progressive recurrent HCV disease, as defined by moderate to severe necroinflammatory activity (grade 3–4) and/or significant fibrosis (stage 2–4) on histologic evaluation.[33] Treatment of recurrent HCV in LT recipients, particularly with successful viral eradication, is associated with a reduced risk of graft failure.[41] Five-year survival has been reported to be significantly greater in patients with SVR than non-responders (93% vs. 69%, respectively).[42]

The majority of data on efficacy and safety of treatment come from retrospective and uncontrolled studies, and few randomized controlled studies have been performed to date.[43–45] The majority of patients included were genotype 1, and most studies employed a reduced dose of RBV (400–800 mg/day) and/or PEG-IFN, as well as hematopoietic growth factors. The pooled estimate of SVR from prospective studies was 24–40%.[4] Biochemical and histological responses were observed in approximately 50% of treated patients. Remarkably, virologic relapse occurred in a substantial

proportion (21–43%) of LT recipients who achieved end-of-treatment response.[19,43,44] Two-thirds of patients required dose reductions of either IFN or RBV and one-fourth discontinued treatment early.[3] Baseline factors associated with SVR included non-1 genotype, previously untreated, low baseline HCV-RNA, adherence to therapy, and donor *IL28B* genotype CC.[8,10,21,43,45–47] On-treatment predictors matched those in the non-transplant setting; achievement of rapid virological response (RVR) was a good predictor of SVR, and failure to achieve EVR was highly predictive for non-SVR.[43,48]

The use of DAA with PEG-IFN and RBV in the management of post-transplant recurrent HCV is challenging. As in non-cirrhotic cases, one could speculate that DAA might also improve SVR rates in HCV patients in the post-LT state. However, caution must be exercised due to limited data on efficacy and safety of DAA in this population.

Another challenge in utilizing DAA in LT recipients is the potential drug interaction with immunosuppressive agents. TVR and BOC, as well as many other DAAs, are substrates and possibly weak inhibitors of cytochrome P450 3A4.[4,49] Lessons from HIV patients have demonstrated that protease inhibitors, particularly when boosted by ritonavir, can lead to a profound increase in serum levels of calcineurin inhibitors and sirolimus.[50] A recent pharmacokinetic study demonstrated that co-administration of telaprevir significantly increased the dose-normalized exposure (AUC) and terminal elimination half-life ($T\frac{1}{2}$) of both cyclosporine (CSA) (AUC increased ~4.6-fold; mean $T\frac{1}{2}$ increased from 12 to 42 hours) and tacrolimus (TAC) (AUC increased ~70-fold; mean $T\frac{1}{2}$ increased from 40.7 to 196 hours).[51] Subsequent clinical studies have demonstrated that BOC and TVR could be administered in LT recipients with close monitoring of immunosuppressive drug levels.[52–57] BOC induced a reduction in the estimated oral clearance of CSA of 50%, of TAC of up to 80%, and of everolimus of 50%.[53,56] With TVR, the doses of CSA, sirolimus, and TAC were reduced by 2.5, 7, and 22-fold, respectively.[55] A recent multi-center cohort study included 37 HCV+ LT recipients treated with BOC (n = 18) or TVR (n = 19) and noted ETR rates of 72% (13/18) and 40% (4/10), and SVR12 rates of 20% (1/5) and 71% (5/7) with TVR and BOC, respectively. The doses of CSA (1.8±1.1-fold with BOC and 3.4±1.0-fold with TVR) and TAC (5.2±1.5-fold with BOC and 23.8±18.2-fold with TVR) were reduced in all patients during the treatment. The most common adverse effect was anemia (92%). Treatment was discontinued in 16 patients (43%) (11 due to treatment failure and 5 due to adverse events). Infections occurred in 10 patients (27%), with three fatal outcomes (8%). Another smaller series reported a SVR rate of 56% (5/9) with TVR-based triple therapy for LT recipients with recurrent HCV (most of them were previously treated with PEG-IFN/RBV).[58]

There is limited data on the interaction between DAA and mammalian target of rapamycin (mTOR) inhibitors. Recognizing that sirolimus carries a black box warning for use in LT,[59] it may be sensible to avoid this agent altogether in patients receiving TVR or BOC.[52] Consideration might be given to everolimus use in place of sirolimus if an mTOR inhibitor is indicated.[52] The shorter half-life of everolimus may make management of drug-drug interactions easier than sirolimus.[52]

Newer generations of DAA are associated with higher potency, more convenient dosing, and less drug-drug interactions, characteristics that are necessary and ideal for use in LT recipients.[49] Simeprevir and faldeprevir are mild-moderate

CYP3A4 and OATP1B1 inhibitors, which are likely to have potential but mild drug-drug interactions with calcineurin inhibitors and other OATP1B1 substrates.[49] Therefore, a small change in calcineurin inhibitor level, as well as unconjugated hyperbilirubinemia, may be expected.[49] Daclatasvir is metabolized by hepatic CYP3A without clinical evidence of CYP3A inhibition or induction,[49] and sofosbuvir is excreted by the kidney. Although these two protease inhibitors are not expected to lead to clinically significant drug-drug interactions in LT recipients, confirmatory studies are needed.[49] Of importance are the recent preliminary results of a multi-center, open-label Phase 2 Study (N=40) evaluating 24-week sofosbuvir plus RBV for treatment of established HCV recurrence after LT found at week four and at the end of treatment that all participants had undetectable HCV-RNA.[60] Four weeks after completing treatment, 77% still had sustained viral suppression (SVR4). No baseline factors were found that predicted which patients would relapse.[60] While these response rates are promising, it is still early to estimate the rate of SVR as relapse could occur four weeks after cessation of therapy. Serious adverse events were reported in 15% of patients (5% led to treatment discontinuation), and no interactions were reported between sofosbuvir and any immunosuppressive agents.[60]

Taken together, DDA-based therapy is feasible for LT recipients with severe HCV recurrence.[54,57,58] Higher rates of SVR (more than 50%) can be expected with BOC- and TVR-based therapy, but close monitoring for side effects and immunosuppressive drug levels are warranted. The use of newer protease inhibitors, such as simeprevir, faldeprevir, daclatasvir, and sofosbuvir, will likely be associated with improved SVR rates in LT recipients as well as fewer drug interactions and side effects. However, optimization of agents and duration of therapy will require further study, and it is likely that IFN-free regimens will be associated with a better safety profile in this population. Recently, cases of severe recurrent cholestatic HCV following LT that were successfully managed by daclatasvir plus PEG-IFN/RBV for 24 weeks[61] and daclatasvir plus sofosbuvir (without IFN) for 24 weeks[62] have been reported. In both, the treatment regimens were well-tolerated, and calcineurin inhibitors trough levels reached the targeted therapeutic range during and after treatment.[61,62] Based on available data, the interactions and dosing strategies of currently-approved concomitant protease inhibitor and immunosuppressive agents during HCV therapy are summarized in Table 2.

Special aspects of HCV treatment after LT

Rejection and autoimmune complications

HCV infection itself is associated with a variety of auto-immune phenomena.[63] Due to the potent immunomodulatory effects of IFN, the risk of graft rejection and other immune complications remain a concern. Additionally, it has been suggested that the improvement in hepatic microsomal function during antiviral therapy may lead to a decrease in serum levels of immunosuppressive agents, which in turn may place patients at a higher risk for ACR.[64] The reported incidence of ACR following IFN-based therapy in HCV-positive LT recipients ranges from 0–25%.[4] Among controlled studies, the occurrence and severity of ACR was not significantly different from that of untreated HCV-positive LT recipients.[64] A typical manifestation of ACR during IFN-based therapy is a secondary increase in serum transaminases after an initial improvement with treatment and concomitant low or negative serum HCV-RNA.[64] Nevertheless, this is neither specific nor sensitive, and the accurate diagnosis of ACR requires prompt liver biopsy. Mild forms of ACR can be managed by augmenting baseline immunosuppression, while moderate/severe form of ACR may require high-dose intravenous corticosteroids. The question of whether or not antiviral therapy should be discontinued at the onset of ACR, particularly in those responding to therapy, remains unclear. Intuitively, it appears that a safe strategy would be to discontinue HCV therapy, unless ACR evolved with low trough levels of immunosuppressive agents, and their doses have been augmented. In that case, HCV therapy can be continued or restarted after ACR has been treated.

Chronic rejection (CR) is a rare but serious complication in LT recipients. The incidence of CR in HCV-positive LT recipients varies between 4–8% in the absence of treatment.[65] Several uncontrolled studies have suggested that CR may be related to IFN-based therapy (incidence range 4–17%).[64,66] CR is generally detected after one year of therapy and is often observed concurrent with the absence or low

Table 2. Empiric recommended dosing strategies of concomitant protease inhibitors and immunosuppressive agents during HCV therapy [Adapted from Charlton M, Dick T. J Hepatol 2014;60:6–8.)

Drug	Mechanism of interaction and exposure effect	Empiric dose changes[*]			
		BOC	TVR	SMV	SFV
Cyclosporine	Inhibits CYP3A4: ↑ drug exposure	↓ 50%	↓ 75%	No data (small ↓)	Not necessary
Tacrolimus	Inhibits CYP3A4: ↑ drug exposure	↓ 75%	↓ 90%	No data (small ↓)	Not necessary
Sirolimus	Inhibits CYP3A4: ↑ drug exposure	Black box warning for use in liver transplant. Recommend everolimus, if mTOR inhibitor indicated.			
Everolimus	Inhibits CYP3A4: ↑ drug exposure	↓ 50%	Likely ↓ 75%	No data (small ↓)	Not necessary
MMF	No published data, no change known	No empiric dose adjustments necessary			
Azathioprine	No published data, no change known	No empiric dose adjustments necessary			
Prednisolone	No published data, no change known	No empiric dose adjustments necessary			

[*]Empiric dose changes should be done in conjunction with therapeutic drug monitoring.
Abbreviations: BOC, boceprevir; TVR, telaprevir; SMV, simeprevir; SFV, sofosbuvir; CYP3A4, cytochrome P450 3A4; mTOR, mammalian target of rapamycin; MMF, mycophenolate mofetil

levels of hepatitis C viremia. Notably, the majority of patients had not experienced ACR during treatment and yet evolved to CR.[64] As in ACR, the diagnosis of CR requires liver biopsy. The pathogenesis of CR remains unclear, and most patients who had graft failure secondary to CR required RT.[64] It should be noted that IFN-related CR may be partly preventable by ensuring that the immunosuppressant dose is not reduced during antiviral therapy.[66]

Autoimmune hepatitis (AIH)-like hepatitis after LT has been reported in HCV patients, particularly with IFN-based therapy.[19,64,67] The histological hallmarks can somewhat resemble classical AIH, including plasma cell-predominant periportal infiltrates with interface hepatitis or so called plasma cell-rich hepatitis. Increased serum transaminase levels are seen during, or after HCV therapy, or in some cases, without a history of antiviral therapy. Autoantibodies are often absent or present with low titers. The majority of cases rapidly respond to increased immunosuppression with or without discontinuation of antiviral therapy.[19,64,67] Adding everolimus may also be an option.[68] Whether this AIH-like hepatitis is a variant of ACR or is *de novo* AIH is a matter of debate.[67]

Immunosuppressive regimens

The impact of immunosuppressive agents on HCV viremia, histologic recurrence, and treatment outcomes has been extensively debated. Immunosuppressive agents may facilitate HCV replication and enhance HCV disease progression. High-dose intravenous corticosteroid for the treatment of ACR has been accompanied by a transient increase in HCV-RNA and an increased incidence of severe HCV recurrence.[2,3] However, in a randomized controlled trial of 312 HCV+ LT recipients with a steroid-free arm (induction by daclizumab), there were no differences in HCV recurrence and graft survival between steroid-free and steroid utilizing regimens.[69] Therefore, there is no indication, specifically for HCV, to avoid oral corticosteroids in the early postoperative period.

Treatment of steroid-resistant ACR with anti-CD 3 monoclonal antibody, OKT3, is a strong risk factor for both the time to development and the severity of recurrent HCV.[2,3,9] Based on limited data, other induction antibody therapies, such as anti-thymocyte globulins (ATG), anti-lymphocyte globulins, daclizumab, and basiliximab, have been noted to have little effect on recurrent HCV.[2,3,9]

Some immunosuppressive agents have antiviral and anti-inflammatory properties, which may in turn alleviate HCV disease progression. Cyclosporine A (CSA) has been shown to have antiviral effect against HCV by inhibiting interactions between cyclophilin B and NS5B-RNA-dependent-RNA polymerase. This effect has not been demonstrated with TAC. Whether this *in vitro* data can translate into the clinical arena remains controversial. In a randomized controlled trial of 95 HCV+ LT recipients comparing CSA-based and TAC-based regimens, CSA was associated with lower rates of severe HCV recurrence (46% vs. 80%) and graft loss (6% vs. 13%, respectively) after a three year follow-up.[70] However, a recent prospective controlled trial (253 HCV+ LT recipients) with seven year follow-up reported conflicting results. There was no significant difference in severity of HCV recurrence, SVR rates (in those 69 patients who received antiviral therapy), and graft and patient survival between CSA and TAC groups.[71] Recent meta-analyses suggested no difference

in HCV recurrence between TAC and CSA regimens, but TAC increased graft and patient survival in HCV transplanted patients.[72] Interestingly, a synergistic role of CSA in combination with antiviral therapy has been suggested. Sugawara *et al*. reported on 21 living-donor LT patients with HCV recurrence that were treated with PEG-IFN/RBV while maintained on a TAC-based regimen. Among eight patients who had no virologic response after six months of treatment and were switched from TAC to CSA, five patients (63%) became HCV-RNA negative within three months of conversion.[73] Recently, a pilot study from Firpi *et al*. randomized 38 patients with HCV recurrence treated with TAC to either continue TAC or switch to CSA before initiation of PEG-IFN/RBV.[74] A modest HCV-RNA drop with a trend toward better virologic responses in the CSA group was observed; although statistical significance was not reached.[74] Taken together, the impact of CSA on HCV recurrence or on antiviral therapy response appears to be neutral or beneficial.[4] Therefore, the utilization of CSA in all HCV+ LT recipients must be deliberated with the caveat that TAC appears to be an overall better immunosuppressive agent.[72,75] The strategy to switch from TAC to CSA before antiviral therapy needs to be further validated.

Data from *in vitro* studies suggest that mycophenolate mofetil (MMF) could have an antiviral effect against HCV through inhibition of inosine monophosphate dehydrogenase (IMPDH) and enhance the effect of CSA and IFN-based therapy.[3,76] However, neither an effect on HCV-RNA nor serum transaminases has been clearly demonstrated in clinical studies.[3,76] An analysis from United Network of Organ Sharing/Scientific Registry of Transplant Recipients (UNOS/SRTR) database suggests that addition of MMF to TAC-based regimen is associated with improved long-term outcomes after LT in patients with and without HCV.[77] A randomized, multicenter trial conducted in Japan (N=75) comparing TAC plus MMF to TAC plus steroids in HCV+ recipients of living donor LT has reported similar outcomes (survival, ACR, recurrent HCV and HCC) at five years in the two groups.[78]

mTOR inhibitors, such as sirolimus and everolimus, have anti-proliferative, anti-inflammatory, and possible antiviral effects, which may translate to a lower rate of HCV disease evolving to cirrhosis.[79,80] A retrospective analysis of 141 HCV+ LT recipients demonstrated that a sirolimus-based regimen did not significantly delay the time to develop severe recurrence of HCV after LT.[79] In contrast, in a prospective cohort of 67 patients (39 received sirolimus, 28 received calcineurin inhibitors), the sirolimus group had significantly lower HCV-RNA levels and increased survival.[81] In addition, two independent retrospective studies (N=1274 and 313) have demonstrated with sirolimus a reduction in the degree of fibrosis and the rate of progression in HCV+ LT recipients.[82,83] However, an analysis of 26,414 patients (12,589 with HCV) in the UNOS/SRTR database suggested a link between sirolimus use and risk of death and graft loss after LT in HCV patients that was not seen in patients without HCV.[84] These conflicting data warrant further and well-designed longitudinal studies to delineate the impact of sirolimus on HCV recurrence.

Donor and recipient genetic background

Genetic variation in the *IL28B* gene, which encodes the antiviral cytokine IFN-ë3, is strongly associated with SVR in

patients with chronic HCV infection treated with PEG-IFN/RBV. A genome-wide association study of more than 1,600 patients infected with HCV genotype 1 found the rate of SVR following PEG-IFN/RBV treatment to be approximately 80%, 40%, and 25% in *IL28B* genotypes CC, CT, and TT, respectively.[85] Following LT, *IL28B* polymorphisms have been associated with histological recurrence and treatment response.[8,10,46,47] Recipient CC genotype has been shown to be an independent predictor of delayed HCV recurrence at two and five years after LT and was associated with slower progression of fibrosis.[8,10] Following HCV recurrence, treatment response has a stronger association with the CC genotype of the donor than the recipient.[21,46,47] Although *IL28B* polymorphisms predict post-LT recurrence and clearance of HCV, these findings have not yet been demonstrated to improve graft or patient survival. Therefore, the use of *IL28B* in donor selection, particularly in the context of live donor LT and in the management of HCV, warrants further study.

Retransplantation (RT)

Following HCV recurrence after primary LT, RT remains the only option for patients with decompensated cirrhosis. Regardless of HCV status, RT is associated with decreased patient and graft survival compared with primary LT.[86] However, it is unclear whether HCV is an independent risk factor for survival or not. It is generally accepted that progression to cirrhosis is faster after RT than after primary LT, particularly in patients with severe hepatitis C recurrence (cholestatic hepatitis and graft failure within the first year).[86] UNOS data from 1994–2005 demonstrated that despite improved outcomes with RT overall, HCV patients continue to have worse patient and graft survival rates compared to non-HCV patients.[87] Additional variables such as increased severity of illness pre-RT may account for decreased survival in this group following RT. As a result, the role of RT in HCV+ LT recipients remains controversial due to concerns of accelerated recurrence leading to rapid graft loss. A score specifically designed for to predict survival after RT for HCV has been proposed.[88] This score includes variables from the first transplant (recipient age), second transplant (donor age, creatinine, INR, and serum albumin), and the interval between both transplants. The area under the ROC (receiver operating characteristic) curve was 0.643 at three years, and survivals were 71%, 56%, and 37% for scores <30, 30 to 40, and >40, respectively.[88] In an era of organ shortage, the use of well-validated prognostic scores is recommended to limit RT to patients with reasonable survival probability.[86]

Conclusions

Management of hepatitis C in LT population presents unique challenges. Suboptimal graft survival in HCV+ LT recipients is attributable to universal HCV recurrence following LT. Eradication of HCV before LT is ideal to prevent HCV recurrence, but is often limited by adverse events, particularly in patients with advanced cirrhosis. Antiviral therapy in LT candidates needs careful monitoring and DAA-based triple therapy is generally not recommended, except by those who have experience with such therapy. Prophylaxis with HCV antibodies is ineffective. Early antiviral therapy after LT has been investigated, but no clear benefit has been demonstrated. Protocol liver biopsy is generally recommended in HCV+ LT recipients, and antiviral therapy may be considered in those with severe/progressive HCV recurrence. SVR can be achieved in approximately 30% of LT recipients with PEG-IFN/RBV. However, adverse effects are common and about one-quarter of patients discontinue treatment prematurely. Survival benefit is evident in those patients who achieve SVR. Favorable patient characteristics for response to therapy include non-1 genotype, previously untreated, low baseline HCV-RNA, and donor *IL28B* genotype CC. DAA-based triple therapy is associated with higher rates of SVR, but with similar or slightly higher rates of side effects, and immunosuppressive regimens need to be adjusted and closely monitored for the levels during the treatment period. Notably, the safety and efficacy of HCV treatment are very likely to improve with newer generation DAA. The impact of immunosuppressive strategy on the natural history HCV recurrence has not been well elucidated. Based upon available evidence, CSA, MMF, and sirolimus appear to have a neutral or small beneficial impact on HCV recurrence. Donor *IL28B* polymorphisms appear to impact the course and treatment outcomes in recurrent HCV. Retransplantation should be considered for patients with reasonable survival probability.

Conflict of interest

None

Author contributions

Literatures reviewing, manuscript drafting, figures and tables creating (CB), conceptualization and critically revision of the manuscript (KRR).

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