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New perspectives for preventing hepatitis C virus liver graft infection

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Abstract

Hepatitis C virus (HCV) infection is a leading cause of end-stage liver disease that necessitates liver transplantation. The incidence of virus-induced cirrhosis and hepatocellular carcinoma continues to increase, making liver transplantation increasingly common[1–3]. Infection of the

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Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published from January, 1995, to January, 2016, by use of the terms “hepatitis c”, “transplantation”, “HCV”, “liver graft”, and “cirrhosis”. Relevant presentations of upcoming publications were identified at the EASL International Liver Congress and the AASLD Liver Meeting. Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles published in English, French, and German were included.

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engrafted liver is universal and increases progression to advanced liver disease, with 20–30% displaying cirrhosis within 5 years. While treatments of chronic HCV infection have improved dramatically, albeit with remaining challenges of failure and access, therapeutic options to prevent graft infection during liver transplantation are emerging. Recent developments in directed use of novel direct-acting antiviral (DAA) agents[4–6] to eliminate circulating HCV prior or following transplantation bring renewed hope for prevention and treatment of liver graft infection. Identifying the ideal regimen and use of DAAs reveals new paradigms of treatment for this special population[6–8]. Complementing DAAs, entry inhibitors have been shown to prevent liver graft infection in animal models[9–13] and delay graft infection in clinical trials[14], providing a perspective to be used concomitant to transplantation. We review the challenges and pathology associated with HCV liver graft infection, highlight current and future strategies of DAA treatment timing, and discuss the potential role of entry inhibitors that might be employed synergistically with DAAs to inhibit graft infection.

Introduction

Hepatitis C virus (HCV) infection is the etiologic agent necessitating more than half of all liver transplantations (LTs) in North America and Europe[15–19]. The engrafted liver universally becomes infected and undergoes rapid progression to serious liver disease; HCV infection is thereby associated with the poorest post-transplantation survival rates compared to other etiologies leading to LT[20]. The even more accelerated natural history of allograft HCV in patients undergoing re-transplantation has made re-transplantation an ethically challenging proposition. Recently developed direct-acting antiviral (DAA) therapies have proven effective in treating chronic HCV infection, and appear more effective in the LT setting than conventional interferon (IFN)-based treatments in genotype 1 patients. However, treatment options are still limited for those needing LT consequent to HCV infection, as transplantation requires immunosuppressive reagents to avoid graft rejection with potential drug-drug interactions, the diminished health of this patient population, and the metabolic burden placed on the newly engrafted liver by co-administered pharmaceutical agents.

The most straightforward means of avoiding the pathogenesis of liver graft infection would be to instate preventative measures to avoid graft infection, but the strong efficacy of current DAAs may allow withholding antiviral treatment during operative stage and addressing HCV infection post-operatively. Here, we review the specific hurdles associated with HCV infection in LT, evidence supporting treatment strategies of patients needing transplantation, and the outlooks for prophylactic measures against liver graft infection.

Challenges of HCV liver graft infection

Universal graft infection in HCV RNA positive patients

Due to the current burden of HCV on transplants, the new potent DAAs are hoped to reduce transplantation activity, preemptively reducing the numbers of patients presenting with hepatocellular carcinoma (HCC) and decompensated cirrhosis[21]. To achieve this goal, however, comprehensive screening is necessary, since the majority of patients with chronic HCV infection only seek medical care following liver-related complications[22]. A positive

outlook is warranted given that a recent analysis indicates that a >90% decline in total infections by 2030 could be achievable, though this will require a 3 to 5-fold increase in diagnosis and treatment[23]. However, the public health strategy approaching this widespread problem must remain to hope for the best while planning for the worst.

HCV recurrence after LT remains universal in patients with detectable serum HCV RNA pre-transplantation. Even patients who are below detection levels for serum HCV RNA on therapy prior to transplantation have a 30% incidence of relapse, excluding those proven to have sustained virological response (SVR) to therapy for an extended period[24]. HCV recurrence is a critical medical problem and responsible for an increased risk of death and of graft failure. Positive detection of HCV RNA in recipients prior to transplantation associates with a diminished 5-year patient survival (69.9% *vs.* 76.6%, P<0.0001) and allograft survival (56.8% *vs.* 67.7%, P<0.0001)[25]; reinfection is a serious problem not only for the recipient, but also taxes the precious resource of suitable donated organs.

Rapid fibrosis progression after liver transplantation

The diminished 5-year survival rate is attributed to an accelerated development of pathology due to the immune-suppressive agents administered to prevent graft rejection. While the average time of progression from initial HCV infection to cirrhosis is about 30 years, 20–30% of transplant recipients develop cirrhosis within 5 years[26]. While only 30% of non-transplant cirrhotic patients have liver decompensation after 10 years of cirrhosis, more than 40% of graft recipients decompensate within the 12 months following LT, of whom less than 50% survive the following year. While the progression to fibrosis in the context of HCV recurrence varies widely depending on individual patient characteristics, the average time of progression to cirrhosis after LT is 10 to 12 years[27]. Re-transplantation is the only therapeutic option to achieve long-term survival of patients with decompensated cirrhosis after transplantation. Due to both poor patient and graft post-transplant survival rates, and the paucity of suitable organ donations, re-transplantation is not a sustainable option in most countries[28].

A critical clinical challenge is to identify scenarios of early and rapid fibrosis development to employ early intervention while minimizing liver damage, highlighting the importance of diagnostic development. The previous consensus opinion was that IFN-based antiviral therapy should be initiated after detecting chronic hepatitis of the liver graft, usually >F1 on the METAVIR scoring system. The diagnosis of HCV recurrence is typically based on liver biopsy detection, since biopsies also can reveal severity of disease progression and exclude other possible diagnoses. It has been recently shown that significant periportal sinusoidal fibrosis in early biopsies (<6 months) is a good predictor of severe HCV recurrence[29]. The use of serum markers that decisively indicate fibrosis progression and other non-invasive techniques that measure liver stiffness will contribute to future decision-making in post-transplantation HCV treatment. Liver stiffness values of <8.7 kPa have a 90% negative predictive value and can be utilized as a threshold in defining significant fibrosis[30]. Pressure levels exceeding 6 mmHg of hepatic venous pressure likewise indicate fibrosis[31].

Robust recurrence of HCV RNA levels soon after transplantation is associated with poor prognosis, so early monitoring of HCV levels is critical. Robust recurrence occurs in 2 to 8%

of patients often resulting in fibrosing cholestatic hepatitis (FCH). FCH is characterized by high levels of cholestatic enzymes and the presence of extensive dense portal fibrosis with immature fibrous bands extending into the sinusoidal spaces, ductular proliferation, cholestasis, and moderate mononuclear inflammation detected in liver graft biopsies[32]. Without response to antiviral agents, FCH typically proceeds to complete liver failure.

Multiple risk factors contributing to rapid and severe fibrosis progression have been identified. High HCV RNA levels in either serum or liver associates with increased progression to cirrhosis, graft loss, and death[33]. Recipient and donor characteristics associated with poor outcome include female gender, donor age, and graft steatosis, while human leukocyte antigen (HLA) matching and IL28B genotype negatively associate with poor outcome[18,34,35]. While some of these factors can be selected for before transplantation, others are unpredictable and only antiviral treatment can improve the prognosis of transplant recipients.

The strategic options of HCV treatment with LT can be divided based on timing of treatment; HCV clearance pre-transplant, inhibition of graft infection concomitant with transplantation, or antiviral treatment after graft infection (Fig. 1).

DAA-based strategies for prevention and treatment of liver graft infection

HCV cure pre-transplant

The clearly optimal tact is to tackle reinfection early by eliminating HCV infection prior to transplantation. This strategy has been difficult to apply until recent DAA approval, since IFN-based therapies have limited efficacy for those with advanced disease while on a transplantation waitlist with SVR being achieved in only 8–39% of cases. The IFN tolerability is generally poor in these patients and contraindicated in patients with decompensated cirrhosis requiring either dose reduction (70%) or early discontinuation (30%) of treatment. The results of a phase 2 clinical study of administration of sofosbuvir with ribavirin (RBV) to 61 patients on waitlists for LT show that this tact with DAAs is effective[6]. Of the 43 patients who displayed viral response prior to transplantation, 70% maintained viral clearance 12 weeks post-transplantation. However, the efficacy of this strategy is genotype dependent and managing DAA combinations in the pre-transplant period is challenging. The use of sofosbuvir/RBV in advanced cirrhosis may contribute to lactic acidosis in approximately 14% of patients[36]. Charlton et al. investigated in the SOLAR-1 trial including the NS5A inhibitor ledipasvir in combination with sofosbuvir and RBV for individuals with cirrhosis and moderate or severe hepatic impairment due to genotype 1 and 4 infections[37]. SVR-12 was achieved in 86–89% in this difficult-to-treat cohort. The inclusion of ledipasvir or daclatasvir with sofosbuvir and RBV have been also investigated in the SOLAR-2 and ALLY-1 studies, respectively, focusing on patients with advanced liver disease pre-transplantation or with recurrent HCV post-transplantation[38–40]. In the SOLAR-2 study, patients with the sofosbuvir-sensitive HCV genotypes 1 or 4 were treated for 12 or 24 weeks with sofosbuvir, ledipasvir, and RBV. Preliminary results revealed high SVR rates of 85%–88%, irrespective of treatment duration in genotype 1. Longer treatment duration was superior (SVR rate of 86% vs. 57%) for patients with genotype 4 infection and effective antiviral therapy was associated with improvement in liver histology,

MELD and Child-Pugh (CP) scores[40]. For some decompensated cirrhotic patients, however, MELD or CP scores increased. Searching for prognosis factors of clinical/biological response instead of only viral response is an ongoing and needed area of investigation.

The ALLY-1 phase-III study included 60 patients with advanced cirrhosis treated with daclatasvir, sofosbuvir and RBV[39]. While overall the SVR12 was 83%, response depended on severity of liver disease; 92%, 94% and 56% for CP A, B and C respectively. These findings suggest that further studies are required to define the best therapy management for CP C patients.

While the inclusion of sofosbuvir has had an impact on the management of genotype 1 infection, the use of this drug has less significantly improved treatment for genotype 3 infection. Foster et al. analyzed addition of NS5A inhibitors to sofosbuvir and RBV in patients with decompensated cirrhosis due to genotypes 1 or 3[40,41]. The response rates varied from 44% to 88%, depending on genotype, NS5A inhibitor, and the use of RBV. Adding ledipasvir to sofosbuvir and RBV was inferior to daclatasvir plus sofosbuvir in patients with genotype 3 infection. Over 40% of patients experienced improvement in liver function with a mean improvement of >2 points of MELD score. Overall, these combinations showed excellent efficacy results and safety profiles, although some patients experienced worsening of their MELD scores. However the severity of cirrhosis remains an impediment to response, even with the new combinations of DAAs. Although the combination of sofosbuvir and NS5A inhibitor velpatasvir for 12 weeks provides SVR in over 95% of patients without cirrhosis[42,43], SVR rate was 83% (n=90) in patients with decompensated cirrhosis[44]. However, the addition of ribavirin to this combination improves the SVR rate of 94%, even in cirrhotic patients (n=87)[44].

The critical argument for treatment before transplantation is the prospect of avoiding LT altogether for individuals with liver disease that has not progressed to hepatocellular carcinoma. About 2/3 of patients achieve clinical and biological improvement during treatment in studies enrolling decompensated cirrhotic patients[37,39,44,45]. However, critical review reveals that 1/3 of patients do not improve or worsen during treatment, regardless of virological response. For those who do improve, the difference is often modest with variations of only 1 or 2 points in MELD score. In a recent meta-analysis involving five studies and including 533 patients, 28% experienced an improvement of MELD score over 3[46]. A number of patients do improve to the point where LT is avoidable. A French cohort study that included 183 patients awaiting transplantation showed that of 53 patients with decompensated cirrhosis, 36% had a complete clinical and biological response, meaning a CP A at the end of treatment[45]. The best improvement was in those with the least disease progression: those with baseline CP with an area under the curve (AUC) of 0.81, the CP threshold of improvement being 7.5. This raises further questions, since some patients keep improving over longer periods of follow-up. When considering longer times while being on waitlists for LT, comorbidities need to be considered. Optimum conditions and thresholds have not been defined for removing patients from waitlists. Although we could expect significant improvement for 1/3 of patients, this improvement is more likely for patients with less severe disease. For individuals with more severe disease, one needs to practice caution

since treating HCV in patients to only get partial biological improvement may be deleterious.

Waitlisted patients with HCC, who normally present with compensated cirrhosis, have several approved regimens available albeit with limited efficacy. In fact, treatment may be futile in about 30% of patients considering the rate of dropout before LT and early HCC recurrence after LT[47]. The severe disease state of those on the transplantation list can limit treatment options and the 12 weeks needed to confirm SVR status is not always afforded pre-transplantation. Patients with severe end-stage liver disease prior to LT or who require complicated post-operative treatment are frequently ineligible for pre-emptive interferon therapy.

DAA treatment after HCV graft infection

At present, two therapeutic approaches can be considered after transplantation: the pre-emptive strategy involving treatment in the first month following transplantation, or to hold off treatment until chronic hepatitis is observed. Despite the clear benefits of early treatment, the pre-emptive strategy is historically not employed due to safety and efficacy limitations of initiating IFN-based antiviral therapy during the post-operative period[48–52]. New DAA IFN-free combination therapy revives this strategy although due to the novelty of these therapies, the evidence regarding efficacy is lacking. Factors influencing the future employ of the pre-emptive strategy will depend on safety, cost, and tolerability of next-generation DAAs relative to typical liver graft damage incurred before assessment of HCV recurrence.

On the other hand, treating HCV recurrence has been the standard therapy and until 2011 involved 48 weeks of PEG-IFN and RBV treatment. Three systematic reviews have reported an SVR rate in these conditions of only approximately 30% with limitations of tolerability including bacterial infections, haematological toxicity, and graft rejection[53–55]. Early virological response (EVR) is a major predictive factor associated with SVR[56,57]. However, effective antiviral treatment post-transplantation has clear benefits in preventing disease progression[58–63]. First-generation protease inhibitors, telaprevir or boceprevir, were the initial agents tested in treating recurrent HCV post-transplantation. Their inclusion with PEG-IFN and RBV improved SVR rates by 50–65% in genotype 1 HCV-infected recipients however with a worse safety profile and potent drug-drug interactions[64,65]. Although feasible, these regimens required close monitoring and great expertise of caregivers leading to their retirement. The new generation of DAAs has further changed the treatment landscape in post-transplantation antiviral treatment, demonstrated in two studies where the initiation of treatment was a year after liver engraftment. Sofosbuvir plus RBV treatment has a 70% efficacy rate in yielding SVR, roughly equivalent to the virological response seen when clearing the virus pre-transplantation [6]. Although this response efficacy is not optimal, it demonstrates efficacy and tolerability even in the most severe patients[66]. However, a more complex cocktail of DAAs can be more efficacious, and several studies describing this have already been communicated and/or published, summarized in Table 1. Data simultaneously comes from both open-label studies and real-life cohorts (HCV-TARGET and CUPILT studies). The SVR 12 rates are usually >90%, better than SVR12 rate treating decompensated cirrhotic prior to LT, and tolerance is excellent. In the SOLAR-1 study

assessing post-transplantation treatment, progressive liver disease was associated with lowered response, however all 6 individuals that had FCH achieved SVR 12 weeks after the end of treatment[37]. Although the treatment of HCV in transplant patients has been significantly improved and simplified, several issues remain to be clarified. This shows the promise of DAAs and combinatorial therapy; multiple targets and mechanisms of action synergize to eliminate the virus.

The optimal duration of therapy remains to be defined. While a number of risk factors of treatment failure were identified for IFN-based regimens, no risk factors have been identified for new DAAs except genotype 3. In the non-transplant setting, most studies comparing different treatment durations did not show any benefit of longer treatment and better adherence, fewer side effects, and lower cost associated with a shorter duration. In the transplant setting, robust data is currently lacking and many studies conservatively use 24-weeks of treatment in this special population until more evidence is collected.

The use of RBV in future regimens is not yet established and could be abandoned once next-generation DAAs with higher efficacy are added. There remains a significant benefit of RBV in patients with severe liver disease and recurrent HCV post-transplantation[41,67,68].

In LT patients, renal impairment is common and should be properly evaluated before initiating antiviral therapy, especially sofosbuvir-based regimens[69]. The metabolism of sofosbuvir is renal and its use is not recommended in patients with creatinine clearance below 30 ml/min until an appropriate dosage is determined. A Phase IIb, open-label study of 200 mg or 400 mg sofosbuvir and RBV for 24 weeks in HCV genotype 1 or 3 patients, and ledipasvir/sofosbuvir in individuals with genotype 1 and 4 infection with renal insufficiency is ongoing (Clinicaltrials.gov:NCT01958281). For other available DAAs, the metabolism is hepatic. Although no detrimental effect is expected in RBV-free combination, in a recent communication of the ANRS C023 CUPILT group, a slight but significant reduction in creatinine clearance during treatment was reported (from 72.7±29.0 to 66.3±25.7mL/min. between baseline and end of treatment; $p<0.0001$) using the combination of sofosbuvir and daclatasvir[70]. But it should better define which patients who worsen. In a recent multicentre trial of LT recipients with recurrent HCV infection treated with sofosbuvir based regimens, renal improvement was observed in the majority (58%) of patients [71]. Those patients with SVR at 12 weeks post-treatment were more likely to have renal improvement, indicating that HCV affects renal health[71].

Drug-drug interactions between DAAs and immunosuppressive drugs, mainly calcineurin inhibitors, remain a concern with these regimens. Simeprevir, a second generation protease inhibitor, is a partial cytochrome P450 (CYP) 3A inhibitor. Since the immunosuppressant cyclosporine is likewise a partial CYP3A inhibitor, combination results in accumulation of both drugs in the blood, and coadministration is discouraged[72]. Ombitasvir, paritaprevir, ritonavir, and dasabuvir require dosing modifications for calcineurin inhibitors tacrolimus and cyclosporine[73,74]. Conversely, sofosbuvir, ledipasvir and daclatasvir do not seem to interact with calcineurin inhibitors[73]. However, close monitoring before, during and after DAA therapy remains essential. In the ANRS C023 CUPILT study, 59% of 130 patients

treated with sofosbuvir and daclatasvir after LT had to change dosage of one immunosuppressive drug during therapy[70].

Finally, the optimal timing for initiation of therapy post-transplantation remains to be determined. Antiviral therapy is usually initiated only when histologically proven recurrent HCV occurs (fibrosis stage ≥2 on the METAVIR score or severe and rapid progression of fibrosis as observed in cholestatic hepatitis). This decision was based on the tolerability of the classic IFN-based regimen, which required post-transplantation recovery time to regain health. Development of IFN-free therapy allows treatment of patients earlier after LT without waiting for disease markers indicating HCV recurrence. This strategy is reasonably based, but without scientific evidence of its efficacy. Nonetheless, earlier treatment appears safe and effective and the potential risk in allowing fibrosis progression on liver graft could raise ethical issues. Treating early after LT could help to overcome the issue of differentiating HCV recurrence and rejection and it could also prevent rejection episodes induced by viral clearance while immunosuppressive levels are still high at early stages after LT. It has been reported that immunosuppressive levels decrease significantly in patients responding to antiviral therapy as the viral clearance improves hepatic microsomal function and elevated regulatory T cell levels may decline[75].

Perspective for prevention of graft infection concomitant with transplantation: HCV entry inhibitors

Viral entry has been demonstrated to play an essential role during re-infection of the graft after LT[76,77]. Thus, concomitant treatment of safe and effective entry inhibitors, including virus-targeting neutralizing antibodies (nAbs), during and immediately after transplantation may prove an effective means of preventing graft infection without allowing allograft damage[78]. This concept is supported by the experience in prevention of HBV graft infection where hepatitis B immune globulin in combination with nucleos(t)ide analogues can reduce HBV recurrence in LT patients to 4%[77,79–81]. Entry inhibitors have been shown to effectively inhibit HCV infection, work synergistically with DAAs, and have proven to be safe and effective in humanized mice[82]. While most of these agents are at a preclinical stage of development, the results of first clinical trials with anti-envelope antibodies[14,83,84] and a small molecule host-targeting inhibitor[85] suggest that they may be future tools in the antiviral arsenal during transplantation. Strategies for blocking viral entry during liver graft infection can either target the virus or host entry factors:

Anti-envelope antibodies

A high rate of viral diversity, glycosylation of the HCV glycoproteins, and association with apolipoproteins aids the escape of HCV from neutralizing antibodies (nAbs)[86–91](reviewed in [89]). In the course of HCV infection, nAbs develop that mostly target regions of E2 that interact with the host receptor CD81[87,92–94]. The crystal structure of the core of glycoprotein E2[95,96] defined the face of the protein where the majority of nAbs bind. Polyclonal and monoclonal nAbs taken from patients with chronic HCV infection or administered by gene therapeutic approaches are capable of inhibiting infection of human liver chimeric mice[9,97–101]. In patients, nAbs targeting the HCV envelope glycoprotein

(MBL-HCV1) effectively delayed viral rebound, proving the principle that immunotherapy will prove an effective addition to the synergistic antiviral arsenal[14]. Current studies are underway in combining MBL-HCV1 with DAAs to optimize therapeutic efficacy of this approach with the latest tools. Recent clinical trials of human HCV immune globulin (HCIG) in combination with DAAs show that administration of the immune globulin is safe and more effective than with DAAs alone[84]. However a potential challenge in utilizing nAbs for prevention of infection is identical to the problem during chronic infection, i.e. genetic adaptation enabling viral escape[14]. Complementing anti-envelope antibodies, small molecules have been identified to interfere with viral entry[102–105].

Host-targeting entry inhibitors

One solution that could feasibly avoid the problem of viral escape from antiviral antibodies would be through targeting host entry factors (Fig. 2)[78,106]. Indeed, infection of HCV variants that escape host anti-envelope antibodies or exhibit resistance to DAAs are effectively blocked by host-targeting entry inhibitors[76,82,107–109], Host-targeting agents have been investigated for multiple steps of viral entry. HCV virions circulate in dynamic complex with lipoproteins and apolipoproteins[110,111]. The earliest step of HCV attachment is mediated by apolipoprotein E binding to heparan sulfates on the baso-lateral surface of the hepatocyte[112]. Inhibitors of heparan sulfate attachment such as the green tea polyphenol epigallocatechin-3-gallate (EGCG) are generally safe and can impair infection in cell culture systems[113,114], although in HCV mouse models the addition of EGCG adds no observable advantage over anti-envelope antibodies alone[115]. The next step of the HCV entry process is interaction of the virion with scavenger receptor B1 (SR-B1). Antibodies to SR-B1 markedly inhibit HCV infection in small animal models[11,13] and prevent antiviral resistance to DAAs[116]. Inhibition of the lipid transfer activity of SR-B1 is sufficient to inhibit infection[117]. A small chemical inhibitor of SR-B1, ITX5061, has been tested in patients undergoing transplantation with HCV infection[85]. Genotype 1 patients under treatment had sustained reduction of viral load, and the genetic variation of the quasispecies was limited[85]. After this initial attachment, a sequence of events takes place including the triggering of signaling pathways involving host kinases such as epidermal growth factor receptor (EGFR) to cluster essential entry factor claudin 1 (CLDN1) and CD81[118,119]. Erlotinib, a small molecule inhibitor of EGFR, has been shown to inhibit HCV infection in both cell culture and animal models[118]. Antibodies that recognize CD81 have also been shown in small animal models to inhibit HCV infection[12,120]. Anti-CLDN1-specific antibodies are not only effective in preventing HCV infection, but can prevent and cure HCV infection in humanized mice in monotherapy without resistance and observable side effects[10,121,122]. The anti-CLDN1 antibody has been shown to be highly synergistic with DAAs[82], prevent antiviral resistance by impairing viral spread[108]. There are a number of other host entry factors such as occludin[123,124], Niemann-Pick C1-like 1 (NPC1L1) [125], transferrin receptor 1[126], and serum response factor binding protein 1 (SRFBP1)[127]. A clinically approved small chemical inhibitor of NPC1L1 has likewise shown efficacy in small animal models and to synergize with DAA[125,128]. Future research will enable the discovery and development of host-targeting entry inhibitors of optimal safety in administration and efficiency in synergizing with DAAs to play a key role in increasing the cure rates in LT.

Advantages and disadvantages

The success of next-generation DAAs in treatment raises the debate of whether HCV entry inhibitors have a place in future clinical practice[128,129]. There are a number of advantages and disadvantages to using entry inhibitors[78,130]. Strengths include their capacity to be used in targeting intervention around transplantation with a short duration of treatment. The barrier for resistance appears to be higher for host-targeting entry inhibitors than for DAA when used in monotherapy[10,108]. Given their complementary mechanism of action to DAAs[106] and efficacy against DAA-resistant viruses[108,131] entry inhibitors may offer a perspective for the patient population who fail preemptive therapy while preventing costly post-transplant therapy. The high level of synergy of entry inhibitors with DAAs observed in cell culture and animal models indicates that these agents could shorten treatment time and circumvent the development of antiviral-resistant variants[10,82,116]. Drawbacks include that a number of entry inhibitors are only now reaching clinical development stages. There are more DAAs in the drug development pipeline that may not be limited by the current safety issues of resistance and complications of renal failure. Targeting host factors will also require careful surveillance of side-effects[106] and viral escape has been described[14,131–134]. Furthermore, the numbers of individuals with serious HCV-related liver disease will decline, as will prices for the DAA regimens.

Other approaches targeting host factors downstream of HCV cell entry[106,135] include microRNA (miRNA) antagonists (antagomirs) or cyclophilin inhibitors [136,137]. A key miRNA that boosts HCV replication, miR-122, acts by shifting HCV genome activity away from translation and toward replication[138]. Antisense agents targeting miR-122 have been shown to be safe and efficient in primate models and patients[139–141]. Cyclophilin, a host factor required for viral replication is efficiently inhibited by alisporivir, a host-targeting agent in clinical development [142]. Whether these strategies are feasible in LT remains to be shown.

Summary and conclusion

Treatment of patients in need of LT as a result of HCV-associated advanced disease is a sensitive and complicated tree of decision-making. The successful use of DAAs as prophylactic and therapeutic agents against HCV infection, both before and following transplantation, promises to assist those likely increasing numbers of individuals who find themselves in this historically difficult-to-treat population. Randomized clinical trials are ongoing to define the role of entry inhibitors in prevention of graft infection.

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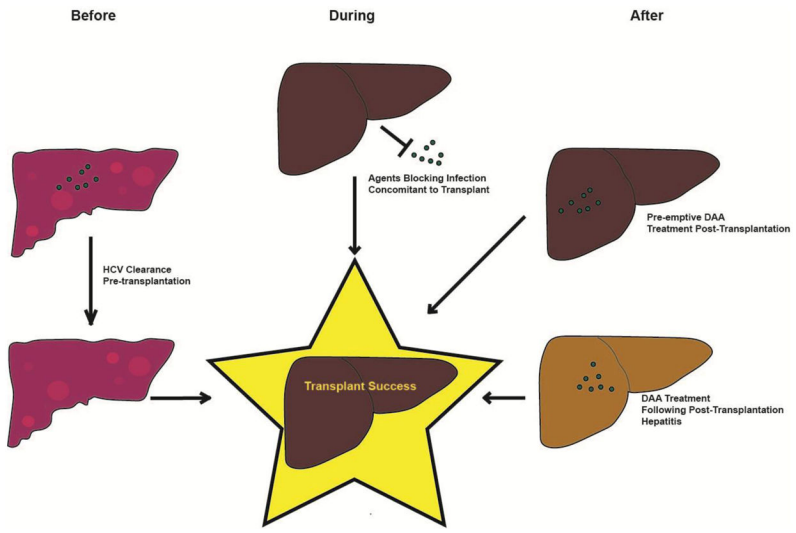

Figure 1. Timing of Antiviral Strategies for Successful Liver Transplantation in HCV-infected Patients

After a patient presents with a cirrhotic liver (upper left) with HCV infection (green dots) there are multiple strategies that have been proposed for having a successful, non-infected transplantation. Successful treatment eliminating the virus before transplantation (lower left) has proven successful to approximately 70% with DAAs[35]. Multiple lines of evidence show that immunoprevention and HCV entry antagonists can play a syngergistic role in blocking infection concomitant to transplantation (center, top). Permitting infection and treating later with DAAs (right top and bottom) has proven 70–97% successful depending on the study and drug employed[53,54].

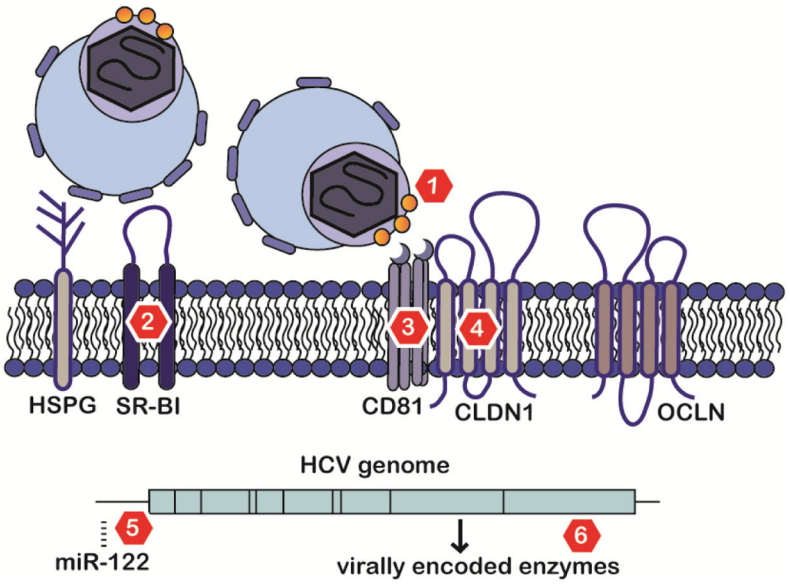

Figure 2. Examples of HCV entry factors as targets to prevent graft infection with completed *in vivo* proof-of-concept

Several points of HCV entry are effective targets to prevent initial or ongoing liver graft infection. The HCV glycoprotein E1/E2 is critical for HCV entry (marker 1), and nAbs binding to E1/E2 have proven effective in animal models and clinically[9,97,100]. Early steps of HCV entry likely involve initial attachment of apoE to HSPG and utilization of SR-B1 (marker 2). SR-B1 inhibitors have been effective in animal models and in the clinic in the context of liver transplantation[11,13,85,145]. HCV E2 directly binds to host entry factor CD81 (marker 3), and antibodies binding CD81 prevent HCV infection in animal models[12,120]. Antibodies recognizing CLDN1 (marker 4) have proven effective in curing animal models of HCV infection[10,121,122]. Furthermore, small molecules erlotinib targeting EGFR[118], a kinase promoting CD81-claudin-1 coreceptor formation, and ezetimibe targeting cholesterol transporter NP1CL1 (not shown) have been shown to inhibit HCV infection in humanized mouse models [125]. Downstream of entry, microRNA 122 (miRNA) antagonists (antagomirs, marker 5) have been shown to effective and safe in animals and patients[139,141]. DAAs targeting virally encoded enzymes have revolutionized HCV treatment (marker 6).

Table 1

Available results of DAA-based regimens to treat HCV recurrence after liver transplantation

Regimen	Study	N	Genotype	Cirrhosis (%)	SVR12	Author (ref)
SOFOSBUVIR+RIBAVIRIN 24 weeks	Prospective Multicenter Open-label	40	All (83% G1)	Yes (40%)	70%	Charlton, M. [65]
SOFOSBUVIR+DACLATASVIR+RIBAVIRIN 12 weeks (ALLY-1)	Prospective Multicenter Open-label	53	All (77% G1)	Yes	94%	Poordad, F. [39]
SOFOSBUVIR+DACLATASVIR±RIBAVIRIN 12 or 24 weeks (ANRS CO23 CUPILT)	Prospective Multicenter Real-life cohort	130	All (82% G1)	Yes (31%)	96%	Coilly, A. [70]
PARITAPREVIR+OMBITASVIR/r+DASABUVIR+ RIBAVIRIN 24 weeks	Prospective Multicenter Open-label	34	Only G1	No	97%	Kwo, PY. [74]
SOFOSBUVIR+LEDIPASVIR+RIBAVIRIN 12 or 24 weeks (SOLAR I and II)	Prospective randomized phase II study	444	G1 (>95%) and G4	Yes (about 50%)	92%	Charlton, M. [37] Manns, M. [38]
SOFOSBUVIR+SIMEPREVIR±RIBAVIRIN 12 weeks	Prospective Multicenter Open-label	109	Only G1	F3–F4 (29%)	90%	Pungpapong, S. [143]
SOFOSBUVIR+SIMEPREVIR±RIBAVIRIN 12 weeks (HCV-TARGET)	Prospective Multicenter Real-life cohort	143	All (80% G1)	Yes (56%)	90% (SVR4)	Sulkowski, M. [144]