Review Article

Management of Hepatitis C Post-liver Transplantation: a Comprehensive Review

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Abstract

Infection with hepatitis C virus (HCV) is a common cause of chronic liver disease, and HCV-related cirrhosis and hepatocellular carcinoma are the leading causes for liver transplantation in the Western world. Recurrent infection of the transplanted liver allograft is universal in patients with detectable HCV viremia at the time of transplant and can cause a spectrum of disease, ranging from asymptomatic chronic infection to an aggressive fibrosing cholestatic hepatitis. Recurrent HCV is more aggressive in the post-transplant population and is a leading cause of allograft loss, morbidity, and mortality. Historically, treatment of recurrent HCV has been limited by low rates of treatment success and high side effect profiles. Over the past few years, promising new therapies have emerged for the treatment of HCV that have high rates of sustained virological response without the need for interferon based regimens. In addition to being highly effective, these treatments have higher rates of adherence and a lower side effect profile. The purpose of this review is to summarize current therapies in recurrent HCV infection, to review the recent advances in therapy, and to highlight areas of ongoing research.

Introduction

Infection with hepatitis C virus (HCV) is a cause of considerable morbidity and mortality. In 2011, an estimated 5.2 million people were living with HCV in the USA; and in 2007, HCV was responsible for over 15,000 deaths.[1,2] HCV is the leading indication for liver transplantation in the Western world and is a prominent cause for both hepatocellular carcinoma and liver cirrhosis worldwide.[3–6] HCV also carries a significant financial burden, with an estimated cost to the USA of $6.4 billion, and a lifetime cost estimated between $64,490 and as much as $270,000 per patient.[7,8]

Over the past few years, promising new therapies have emerged for the treatment of HCV that have demonstrated high rates of viral clearance without the need for interferon (IFN) based regimens. In addition to being highly effective, these treatments have higher rates of adherence and a lower side effect profile. These treatments have become the standard of care in the pretransplant setting and have an expanding role in the post-transplant setting.[9,10] The purpose of this review is to summarize current therapies in recurrent HCV infection, to review the recent advances in therapy, and to highlight areas of ongoing research.

HCV in the transplant recipient

Recurrent infection of the transplanted liver is universal in patients with detectable HCV viremia at the time of transplant, and infection of the allograft occurs within hours of organ transplantation.[11,12] Acute infection manifests in a significant proportion of patients (62% in one study of 149 transplants)[13] and is characterized by high viral titers, characteristic histological changes, and variable transaminitis.[14] Diagnosis is histological, with biopsy showing lobular infiltrates, hepatocyte necrosis, and fatty infiltration.[15] Viral clearance does not occur in recurrent HCV, and patients invariably progress to chronic infection. Severe recurrent HCV can manifest in two ways: as a chronic recurrent HCV infection and as an aggressive fibrosing cholestatic hepatitis (FCH).[16]

The course of chronic recurrent HCV in the immunocompromised transplant recipient is more aggressive than in immunocompetent patients, with 5 year rates of chronic hepatitis and cirrhosis reaching 80–95% and 10–28%, respectively.[14,17–21] Following the onset of cirrhosis, the risk for decompensation at 1 year is 42%, and once decompensation occurs, the 1 year survival rate is as low as 41%.[18] As well as causing considerable morbidity and mortality, HCV recurrence puts further strain on the already scarce supply of donor livers; HCV is responsible for 27–41% of liver retransplantations.[22,23]

Although the majority of post-transplantation HCV manifests as chronic liver disease, a small proportion (10–12%) of patients will develop FCH.[21,24] The diagnosis is made upon fulfillment of all of the following criteria: 1) Greater than

1 month post-transplantation; 2) Serum bilirubin >6 mg/dL; 3) Serum alkaline phosphatase and gamma-glutamyltransferase level >5 times the upper limit of normal; 4) The presence of characteristic histology on biopsy (ballooning of hepatocytes, absence of inflammation, and cholangiolar proliferation without bile duct loss); 5) Very high serum HCV-ribonucleic acid (RNA) levels; and 6) Absence of surgical biliary complications and absence of evidence of hepatic artery thrombosis.[16] The prognosis of cholestatic HCV is poor and typically results in rapid deterioration and death with or without liver transplant.[16,25]

Risk factors for development of recurrent chronic HCV

Intrinsic recipient factors

There are multiple intrinsic factors in liver allograft recipients associated with HCV recurrence. Levels of HCV viremia $\geq 1.0 \times 10^6$ vEq/mL prior to liver transplant were linked with significantly worse graft and patient survival (one study demonstrated RR of 4.3 and 3.6, respectively).[19,26] High viral loads in the first 3 months post-transplant have also been associated with severity of HCV recurrence.[21]

Blasco *et al*. demonstrated that hepatic venous portal pressure gradients (HVPG) are good predictors of clinical decompensation due to HCV recurrence, with only 2% of patients with a normal HVPG and 67% of patients with abnormal HVPG progressing to decompensation.[27] A recent study investigating absolute lymphocyte count (ALC) demonstrated that low ALC pretransplant and at 1 month post-transplant were significantly associated with HCV recurrence. ALC <500/μL also negatively influenced both sustained virological response (SVR) rates and patient survival.[28] Polymorphisms in interleukin-28B (IL-28B) were linked with recurrent HCV; recipients with the IL-28B TT genotype were particularly at risk for severe histological recurrence of HCV.[29,30] Other recipient factors that have been associated with recurrent HCV severity include female sex, race, socioeconomic factors, and severity of disease.[16,26,28,31–34]

The link between cytomegalovirus infection and HCV recurrence remains unclear, with some studies showing an association between CMV and HCV-induced graft failure and cirrhosis,[35–37] and other studies showing no significant association.[38]

Intrinsic donor factors

A number of donor factors have also been linked to HCV recurrence. Advanced donor age was observed to accelerate the progression of fibrosis in the transplanted liver,[28,32,36,39] and the increasing age of donors was associated with a decrease in survival of HCV transplant recipients.[39–41]

The condition of the donor graft has an impact on HCV recurrence; the presence of donor graft steatosis is associated with earlier and more severe recurrence of HCV.[42,43] Ischemia-reperfusion injury could also play a role, with both warm and cold ischemia times being implicated in HCV recurrence, although these findings are not consistent.[28,39,44] The risk of HCV progression has not been linked to the type of donation, with no difference in risk between living donor liver transplants and deceased donor transplants.[45]

Immunosuppression

Immunosuppression post-liver transplantation is unavoidable and has been associated with increased disease severity in HCV recurrence.[46] Berenguer *et al*. not only demonstrated that stronger immunosuppression was linked to worse outcome in recurrent HCV,[40] but that avoidance of potent immunosuppression yielded better patient outcome.[47]

Two of the most commonly used immunosuppressants in liver transplant patients are the calcineurin inhibitors (CNI) cyclosporine and tacrolimus. Numerous studies have investigated outcomes post-liver transplant between these two drugs. In the general liver transplant population, the use of tacrolimus is associated with significantly reduced rates of death, graft loss, acute rejection, and steroid-resistant rejection.[48] However, multiple studies and a recent meta-analysis have demonstrated no correlation between the type of CNI used and the risk of HCV recurrence.[49–52] Corticosteroid use also plays an important role in HCV recurrence. Treatment of acute cellular rejection with multiple boluses of corticosteroids as well as rapid tapering of steroids have both been linked to recurrent disease.[19,53] Reduced progression of recurrent HCV and better patient outcomes were demonstrated with the use of slow tapering steroid regimens.[47,54]

Treatment of HCV post-liver transplant

Successful pretransplantation clearance of HCV-RNA has been shown to prevent recurrence of HCV but has previously been limited by side effects and low success rates.[55,56] The advent of new, highly efficacious treatments for HCV has allowed for clearance of HCV with relatively low side effect profiles, and pretransplantation treatment of HCV will continue to play an important role in the prevention of recurrent HCV.[57] However, successful pretransplant treatment of HCV precludes the use of an HCV-infected allograft, and numerous studies have demonstrated equivalent outcomes using HCV infected donors.[58–61] HCV positive donors represent an important source of transplanted allografts, with 23% of HCV related liver transplants receiving allografts from HCV positive donors.[62] As long as donor livers continue to be scarce, post-transplant HCV is likely to remain a relevant clinical entity despite improved treatments. Two strategies exist for the treatment of HCV post-transplant: pre-emptive treatment of HCV before graft damage occurs and treatment of established recurrent HCV after histological evidence of significant fibrosis.

Until recently, the standard of care for treatment of recurrent HCV was combination therapy with IFN or pegylated IFN (PEG-IFN) and ribavirin (RBV). Dual therapy with these agents improved both patient and graft survival;[63] but treatment carried a high rate of side effects, with SVR rates of only approximately 30%. Significant side effects were common and led to premature discontinuation of therapy in another 30%, mainly attributable to anemias, cytopenias, neuropsychiatric episodes, thyroid abnormality, poor tolerability, and rejection. Dose reductions due to anemias and other cytopenias were also commonly required.[64–66] Pre-emptive treatment of acute recurrent HCV with IFN and RBV has been disappointing, with SVR rates much lower than those observed in treatment of nontransplanted patients with acute HCV infection. Studies have shown an SVR of only 10–25% in the transplant population compared with 90% in the non-transplant population. As with all patients treated with IFN

and RBV post-transplant, there was a high rate of side effects.[67,68]

New treatments

The last few years has seen the introduction of Direct Acting Antivirals (DAAs), with treatments containing telaprevir and boceprevir approved in 2011, sofosbuvir and simeprevir in 2013, and, more recently, daclatasvir, ledipasvir, ombitasvir, paritaprevir, and dasabuvir. American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) recommendations for the treatment of recurrent HCV are summarized in Table 1, and Table 2 summarizes important recent studies on the treatment of recurrent HCV with DAAs.

First generation DAAs

Boseprevir and telaprevir are protease inhibitors that bind HCV nonstructural 3 (NS3) active site. In the post-transplant setting, combined with PEG-IFN and RBV, both drugs have been shown to be more effective than PEG-IFN/RBV dual therapy, with SVRs of 20–71%.[69–72] However, as with the pretransplant population, the use of boseprevir and telaprevir is severely limited by their side effect profile. Especially significant side effects include severe cytopenias, with considerably more than half of all patients requiring the use of erythropoietin or packed red blood cell transfusions to treat severe anemia.[69,71,73] These drugs frequently interact with immunosuppressive agents, such as cyclosporine and tacrolimus, requiring careful monitoring of trough levels and dose adjustment.[69,71,73–77] Renal function is another concern in patients on triple therapy with boseprevir or telaprevir, with approximately 5% of patients developing renal impairment.[78] These drugs are not commonly used in general practice.

Second generation DAAs

Simeprevir (Olysio®) is a once daily HCV NS3/4A protease inhibitor that was initially introduced as a triple therapy with RBV and PEG-IFN. Quantitative Ultrasound Ezetimibe and Simvastatin Trial (QUEST)-1 and QUEST-2 demonstrated the superior efficacy of simeprevir triple therapy over PEG-IFN with RBV in treatment naive HCV genotype 1 patients, achieving an SVR 12 of 80% and 81%, respectively.[79,80] With the exception of one very small trial, simeprevir triple therapy has not been studied in the post-transplant or recurrent HCV population.[81] The use of simeprevir triple therapy is limited by the Q80K (Gln80Lys) polymorphism, which is an NS3 polymorphism that reduces simeprevir's activity against HCV genotype 1a. In QUEST-1, patients with HCV genotype 1a with the Q80K polymorphism gained no benefit with the addition of simeprevir to PEG-IFN and RBV therapy when compared to placebo.[79] There were no specific contraindications to simeprevir, and commonly encountered side effects include rash development (28%), nausea (20%), pruritus (20%), myalgia (16%), and dyspnea (12%). Simeprevir has a number of clinically significant drug interactions, importantly with antiretrovirals used in HIV therapy, cyclosporine, and sirolimus.[82]

Sofosbuvir (Sovaldi®) is an HCV nucleotide analogue NS5B polymerase inhibitor, and combination therapies containing sofosbuvir have now become the standard of care in HCV in the USA.[10] Data from a compassionate use program using a combination of sofosbuvir and RBV in 103 patients with severe recurrent HCV yielded an SVR 12 of 59% when considering all patients and 73% in those with early recurrence.[83] Charlton *et al*. studied sofosbuvir and RBV dual therapy in 40 patients with recurrent HCV in a multicenter, open label study and demonstrated an SVR 12 of 70%. Anemia was seen in 20% patients, with fatigue (30%), diarrhea (28%), and headache (25%) being the most common reported side effects.[84] There have been several reports of the successful use of sofosbuvir and RBV with or without PEG-IFN to treat FCH.[83,85–87]

Overall the side effect profile of the sofosbuvir/RBV combination is considerably better when compared to that of telaprevir and boseprevir triple therapy.[84] In addition, in a study of healthy volunteers, sofosbuvir was not associated with significant changes in the level of cyclosporine or tacrolimus.[88] The recently updated 2014 guidelines produced by AASLD and the Infectious Disease Society of America (IDSA) recommend sofosbuvir and RBV dual therapy for treatment naive patients with genotype 2 or 3 recurrent HCV. EASL

Table 1. Summary of AASLD/IDSA and EASL guidelines for management of post-transplant HCV

Genotype	AASLD/IDSA	EASL
1	Ledipasvir + sofosbuvir + ribavirin for 12 weeks	Sofosbuvir + daclatasvir +/− ribavirin for 12–24 weeks
	Ledipasvir + sofosbuvir for 24 weeks (alternate regimen if ribavirin intolerant or ineligible)	Sofosbuvir + simeprevir +/− ribavirin for 12 weeks (alternate regimen)
	Sofosbuvir + simeprevir +/− ribavirin for 12 weeks (alternate regimen)	–
	Paritaprevir + ritonavir + ombitasvir + dasabuvir for 24 weeks (alternate regimen)	–
2	Sofosbuvir + ribavirin for 24 weeks	Sofosbuvir + ribavirin for 12–24 weeks
3	Sofosbuvir + ribavirin for 24 weeks	Sofosbuvir + daclatasvir +/− ribavirin for 12–24 weeks
4	Ledipasvir + sofosbuvir + ribavirin for 12 weeks	Sofosbuvir + daclatasvir +/− ribavirin for 12–24 weeks
	Ledipasvir + sofosbuvir for 24 weeks (alternate regimen if ribavirin intolerant or ineligible)	Sofosbuvir + simeprevir +/− ribavirin for 12 weeks (alternate regimen)
5	–	Sofosbuvir + daclatasvir +/− ribavirin for 12–24 weeks
6	–	Sofosbuvir + daclatasvir +/− ribavirin for 12–24 weeks

Table 2. Recent studies in recurrent HCV

Treatment	Study name/author	Study type	Number of enrolled patients	Genotype	Fibrosis severity (METAVIR or equivalent fibrosis stage)	SVR 12	Adverse effects
Boceprevir/telaprevir + RBV + PEG-IFN	Coily et al., 2014[70]	Prospective	37	Genotype 1 1a (28%) 1b (72%)	F2 (38%) F3 (46%) F4 (16%)	20% (telaprevir) 71% (boceprevir)	Anemia (92%) Blood transfusion requirement (35%) Infection (27%)
Daclatasvir + sofosbuvir +/− RBV	Pellicelli et al., 2014[94]	Prospective	12	Genotype 1 (92%) 1a (58%) 1b (8%) Genotype 4 (8%)	F4 (75%)	75%	N/A
Boceprevir/telaprevir + RBV + PEG-IFN	Burton et al., 2014[69]	Retrospective	81	Genotype 1 (100%) 1a (56%) 1b (41%) Unknown (4%)	F0-2 (47%) F3-4 (53%)	63%	Blood transfusion requirement (57%) Creatinine increase ≥0.5 mg/dL (38%) Hemoglobin <8 g/dL (21%)
Ombiasvir + paritaprevir + dasabuvir + ritonavir + RBV	Kwo et al., 2014 CORAL-1[101]	Prospective	34	Genotype 1 1a (85%)	F0 (18%) F1 (38%) F2 (44%)	97%	Fatigue (50%) Headache (44%) Cough (32%) Anemia (29%)
Sofosbuvir + RBV +/− PEG-IFN	Forns et al., 2014[83]	Prospective	104	Genotype 1 (82%) 1a (35%) 1b (47%) Genotype 2 (1%) Genotype 3 (7%) Genotype 4 (7%)	N/A	59%	Hepatic decompensation on treatment (18%) Infections (16%) Anemia (10%)
Ledipasvir + sofosbuvir + RBV	SOLAR-1 (preliminary results 2014)[100]	Prospective	223	Genotype 1 1a (71%) 1b (28%) Genotype 4 (<1%)	F0-3 (50%) F4 (50%)	96% (non-cirrhotic) 96% (cirrhotic) 81% (decompensated)	N/A

(continued)

Table 2. *(continued)*

Treatment	Study name/author	Study type	Number of enrolled patients	Genotype	Fibrosis severity (METAVIR or equivalent fibrosis stage)	SVR 12	Adverse effects
Sofosbuvir + RBV	Charlton *et al.*, 2015[84]	Prospective	40	Genotype 1 (83%) 1a (55%) 1b (28%) Genotype 3 (15%) Genotype 4 (3%)	F0 (3%) F1-2 (35%) F3 (23%) F4 (40%)	70%	Fatigue (30%) Diarrhea (28%) Headache (25%) Anemia (20%)
Boceprevir/telaprevir + RBV + PEG-IFN	Verna *et al.*, 2015[72]	Retrospective	45	Genotype 1 1a (57%)	F1 (2%) F2 (11%) F3 (54%) F4 (33%)	51% in advanced fibrosis 44% in FCH	Blood transfusion requirement (56%) Creatinine increase $\geq$0.5 mg/dL (37%) Hemoglobin <8 g/dL (26%) Hepatic decompensation on treatment (24%)
Simeprevir + sofosbuvir +/− RBV	Pungpapong *et al.*, 2015[91]	Prospective	123	Genotype 1 1a (60%) 1b (35%) Unable to subtype (5%)	F0-2 (70%) F3-4 (30%)	90%	Anemia (72% in RBV group, 5% in non-RBV group) Fatigue (13%) Skin complaints (6%) Headache (5%) GI complaints (5%)

Abbreviations: RBV, ribavirin; PEG-IFN, pegylated interferon; FCH, fibrosing cholestatic hepatitis; GI, gastrointestinal; N/A, not available.

currently recommends sofosbuvir and RBV only for the treatment of recurrent genotype 2 HCV.[9,10]

Sofosbuvir is renally excreted and is not recommended in patients with creatinine clearance below 30 mL/min or for those requiring hemodialysis or peritoneal dialysis due to a lack of studies in the area. NCT01958281 is a Phase-2 clinical trial that is currently recruiting and will investigate the safety of sofosbuvir with RBV in the treatment of patients with renal failure and HCV genotype 1 or 3 infection.[89]

Simeprevir and sofosbuvir dual therapy was studied in 167 treatment naive patients with HCV genotype 1 infection in the Combination Of SiMeprevir and sOfosbuvir in HCV genotype 1 infected patientS (COSMOS) trial. SVR 12 was achieved in 92% of patients, with the most common side effects being fatigue (31%), headache (20%), and nausea (16%). In addition, the presence of the Q80K polymorphism did not have a significant detrimental effect on SVR.[90] The efficacy of this combination has also been demonstrated in the post-transplant setting: Pungpapong and colleagues demonstrated that treatment with simeprevir and sofosbuvir with or without RBV was well tolerated and observed an SVR 12 of 90% in 123 patients with recurrent genotype 1 HCV. However, SVR 12 rates were lower in patients with advanced fibrosis and HCV genotype 1a (71% in METAVIR F3-4 and 91% in F0–F2).[91] The AASLD and IDSA have recommended this combination (with or without RBV) as an option for the first line treatment of recurrent HCV in treatment naive patients with HCV genotype 1.[10] EASL extended this recommendation to include patients with genotype 4.[9] The Phase-2 GALAXY study is currently recruiting and will investigate the efficacy and safety of sofosbuvir and simeprevir dual therapy with or without RBV post-liver transplant.[92]

Third generation DAAs

Daclatasvir (Daklinza) is an HCV NS5A inhibitor that is coadministered with sofosbuvir with or without RBV. In the pretransplant population, Sulkowski *et al*. studied daclatasvir plus sofosbuvir in 211 patients with HCV genotype 1, 2 or 3. The SVR 12 was 98% and, like the other new DAAs, the side effect profile was favorable. The most common side effects were fatigue (29–50%), headache (16–38%), and nausea (10–31%).[93] Pellicelli *et al*. studied daclatasvir and sofosbuvir with or without RBV in 12 post-liver transplant patients (including three patients with FCH) in a compassionate use program. They found that although the combination was very effective in clearing HCV infection, mortality was still high, probably due to the severity of underlying liver disease in the patient group studied. Importantly, they also found that no dose adjustment of the CNIs was required.[94] ALLY-1 is an ongoing Phase-3 trial that is investigating daclatasvir, sofosbuvir, and RBV treatment in recurrent HCV.[95] EASL recommends daclatasvir with sofosbuvir with or without RBV as treatment for recurrent HCV genotypes 1, 3, 4, 5 or 6,[9] but daclatasvir is not currently licensed in the USA.

Ledipasvir is an HCV 5S5A inhibitor that is prescribed in combination with sofosbuvir as a dual therapy (Harvoni®). In the nontransplant population, the ION 1–3 trials showed SVR rates of >96% with significantly reduced rates of side effects. The most common side effects were fatigue (18%), headache (17%), and nausea (9%).[96–98] Triple therapy with ledipasvir, sofosbuvir, and RBV has shown promise in the treatment of patients who have failed prior treatment with sofosbuvir-based regimens, with an SVR 12 of 98% in 51 patients,[99] but there

are no studies yet in the post-liver transplant population. Gilead announced results of the SOLAR-1 study at the 65th Annual Meeting of the AASLD. It was a Phase-2, open label study of 223 patients with recurrent HCV (genotypes 1 and 4) post-liver transplant who were treated with ledipasvir, sofosbuvir and RBV. In cirrhotic, noncirrhotic, and decompensated patients, SVR 12 rates were 96%, 98%, and 81%; and SVR 24 rates were 98%, 96%, and 81% respectively.[100] Ledipasvir plus sofosbuvir with or without RBV has recently been recommended by the AASLD as treatment for patients with genotype 1 or 4 recurrent HCV.[10]

The combination of ombitasvir, paritaprevir (ABT-450), dasabuvir, and ritonavir (viekira pak™) with RBV was studied in the CORAL-1 trial, which included 34 liver transplant patients with mild recurrent HCV. The SVR was 97%, and although adverse effects of medication were common, the majority of these were classed as mild or moderate in severity. The most commonly reported side effects were fatigue (50%), headache (44%), cough (32%), and anemia (29%).[101] This combination of drugs has a wide range of drug interactions, notably drugs that are dependent on cytochrome P3A (CYP3A), CYP3A, or CYP2C8 inducers and CYP2C8 inhibitors. Use of these drugs in the post-transplant patient also requires close monitoring of cyclosporine and tacrolimus levels.[102] Ombitasvir, paritaprevir, dasabuvir, and ritonavir quadruple therapy is currently recommended by the AASLD as an alternate treatment option in recurrent HCV genotype 1.[10]

Conclusions

Due to the low success rates and high incidence of significant side effects seen with older HCV therapies, pre-emptive HCV therapy has been avoided; and treatment of recurrent HCV has historically been delayed until the development of significant damage on liver biopsy.[9,16] The introduction of new DAAs reopens the discussion about the theoretical benefit of treating HCV before the development of significant liver allograft damage, and the optimal time for treatment of recurrent HCV has yet to be identified. While pretransplant eradication will continue to play a critical role in the prevention of recurrent HCV, the advent of new drugs that achieve excellent rates of SVR with a low side effect profile in a group of patients who are notoriously difficult to treat heralds a turning point in the management of recurrent HCV.

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Conflict of interest

Dr. Ahmet Gurakar is a consultant for Gilead.

Author contributions

Review of the literature and writing of the manuscript (OM), review of the literature and final editing of the manuscript (AG).

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