

Hepatitis C Recurrence after Orthotopic Liver Transplantation: Mechanisms and Management

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Abstract

Chronic Hepatitis C (HCV) infection is the leading indication for orthotopic liver transplantation and recurrence is nearly universal. Chronic HCV infection is frequently established through evasion of the innate immune system. Priming of adaptive immune responses modulate the severity and rate of fibrosis progression. Those with demonstrable viremia entering the transplant period uniformly suffer recurrence post-transplant. Progression to cirrhosis is accelerated post-transplant secondary to systemic immunosuppression. In addition, a number of factors, including donor, host, and viral characteristics, influence severity and rate of fibrosis progression. Interferon-based therapy, the previous standard of care, in those with advanced cirrhosis or post-transplant has been limited by a number of issues. These include a relative lack of efficacy and poor tolerability with higher incidence of infection and anemia. Recently, approval of direct acting antivirals have ushered in a new era in HCV therapeutics and have applicability in these special populations. Their use immediately prior to or post-transplant is expected to improve both morbidity and mortality.

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Introduction

Chronic hepatitis C (HCV) infection is a major public health problem; with an estimated 180 million people infected worldwide and approximately 4 million infected in the

United States (US).¹ For approximately two decades, therapy has been relatively expensive and difficult to complete. More recently, direct acting antivirals (DAAs) have been developed and are revolutionizing treatment paradigms.² Their timely application prior to the development of cirrhosis is projected to lessen the incidence of end stage liver disease (and associated complications) attributable to chronic HCV infection. In addition, their use is expected to improve outcomes after orthotopic liver transplantation.

Transplantation for hepatitis C virus

HCV infection is currently the leading indication for orthotopic liver transplantation, and it is estimated that approximately one-third of patients on the waiting list for transplant are infected.³ Although the incidence of new infection with progression to cirrhosis may be declining, there has been a concomitant rise in transplant listing for hepatocellular carcinoma (HCC) related to HCV cirrhosis.⁴

While graft and patient survival rates have steadily improved for non-HCV related indications, this is not true for HCV related transplants.⁵ For over a decade, relatively poorer results have been noted for those with HCV indications.⁶ In a recent review of the Organ Procurement Transplant Network/United Network of Organ sharing (OPTN/UNOS), 3 year survival was at 78% for 7,459 anti-HCV positive recipients and 82% for 20,734 anti-HCV negative recipients.⁷ Similar results were reported in Europe: 73% survival in non-HCV recipients compared with only 66% in HCV positive recipients.⁸ Significant interest has focused on reasons for this discrepancy in outcomes with HCV. In this context, systemic immunosuppression and advancing donor age appear to be important.^{9,10} The phenomenon of HCV recurrence after transplant is the driving force for these poorer outcomes.¹¹

HCV reinfection

Reinfection of liver allografts is considered universal and occurs at the time of allograft reperfusion.^{12,13} During the anhepatic phase of transplant surgery, HCV ribonucleic acid (RNA) levels decline to undetectable levels, but after only a few hours, increase rapidly to peak by the fourth post-operative month.¹⁴ At 1 year, HCV RNA levels are generally 1 to 2 logs higher than prior to liver transplant.¹⁵ The diagnosis of recurrent HCV infection requires detection of HCV RNA in serum; and the diagnosis of recurrent disease requires compatible histology as well. Histologic features of liver injury will typically develop after 3 months and resemble those seen in the native liver.¹⁶ Once re-infection is established, the

Keywords: Innate immunity; Fibrogenesis; Sofosbuvir; Simeprevir.

Abbreviations: AASLD, American Association for Liver Disease; ALT, alanine aminotransferase; CMV, cytomegalovirus; CsA, cyclosporine; CTP, Child Turcotte Pugh; CUPIC, compassionate use of protease inhibitors in viral C cirrhosis; DAA, direct acting antiviral; DCD, donation after cardiac death; DDLT, deceased donor liver transplantation; FCH, fibrosing cholestatic hepatitis; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HHV, human herpes virus; IDSA, Infectious Disease Society of America; IGD, immune-mediated graft dysfunction; IL, interleukin; ISG, interferon stimulated gene; LADR, low accelerated dose regimen; LDLT, liver donor liver transplantation; MELD, model for end-stage liver disease; NS, non-structural; Peg-IFN, pegylated interferon; PTVR, post-transplant virologic response; RBV, ribavirin; RNA, ribonucleic acid; SNP, single nucleotide polymorphism; SVR, sustained virologic response; Tac, tacrolimus; Th, T-helper; Treg, t-regulatory; US, United States.

Received: 14 May 2014; Revised: 06 June 2014; Accepted: 07 July 2014

[†] DOI: 10.14218/JCTH.2014.00016.

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disease progresses; and 20% to 54% of liver transplant recipients develop bridging fibrosis-cirrhosis within 5 years post-transplantation.¹⁷ Persistent low level inflammation and loss of viral control mechanisms from systemic immunosuppression account for this accelerated progression of cirrhosis. In addition, co-factors, such as diabetes mellitus (preexisting or promoted by use of calcineurin based immunosuppression), may further promote disease progression. Accelerated progression post-transplant is variable; dependent upon the degree of immunosuppression and a number of patient co-factors and baseline demographics. Variability in the aforementioned manifests through multiple clinical variations of recurrence: ranging from standard "run of the mill" HCV recurrence to the highly lethal, e.g. fibrosing cholestatic hepatitis (FCH).

Clinical presentations of HCV recurrence

"Standard" HCV recurrence

Transition from acute hepatitis to chronic hepatitis usually occurs between 3 and 9 months after transplantation. Transplant recipients may develop histologic features of acute hepatitis C accompanied by a rapid rise in HCV viral load. The most common pattern of recurrence is the evolution over time to chronic hepatitis, as it occurs in immunocompetent patients (albeit at higher levels of viremia and faster progression of fibrosis). Fibrosis can progress linearly, but its course is variable and often unpredictable.¹⁸ Interestingly, a non-Markov analysis based on 901 fibrosis measurements in 401 patients showed that risk of progression decreases as time in a given stage increases.¹⁹ However, a longer time to reach a stage does not predict a lower risk of progressing to a higher stage. Serial biopsies in patients with recurrent hepatitis C have demonstrated annual rates of fibrosis progression between 0.3 and 0.6 stages/year (score F0-F4) versus 0.1 to 0.2 stages/year in immunocompetent patients with chronic hepatitis C.²⁰⁻²² The median interval from transplantation to cirrhosis is 9.5 years versus 30 years from infection until cirrhosis in immunocompetent patients. The best predictor of cirrhosis risk at 5 years is severity of necroinflammatory activity in the allograft at 12 months post-transplant.²³ Often, protocol biopsies are performed by transplant programs to monitor fibrosis progression.

Fibrosing cholestatic hepatitis

FCH is a presentation of HCV largely unique to liver allograft recipients and often occurs within the first year after transplantation. FCH can be present in over-immunosuppressed recipients, and studies typically show homogeneous viral quasispecies and massive HCV RNA levels in the peripheral circulation (usually >30–50 million IU/mL).²⁴ Liver damage in FCH is due to a direct viral cytopathic effect on hepatocytes from massive HCV replication.²⁵ The typical case of FCH HCV is characterized by extensive hepatocyte swelling necrosis, cholestasis, and Kupffer cell hypertrophy in combination with portal expansion due to prominent ductular reaction (often with absent or rare Cytokeratin-7+ intermediate cells) and fibrotic-type interface activity with mild mixed or even neutrophil-predominant portal inflammation.²⁶ The intra-hepatic immune response in FCH HCV is typically T-helper (Th)-2-like; whereas it is Th-1-predominant in conventional recurrent HCV, and the few infiltrating lymphocytes often lack

HCV specificity.²⁷ Apart from immunosuppression, clear risk factors with regard to genotype and patient demographics have not been well established. FCH usually leads to liver failure/graft loss within 1 to 2 years after transplantation.

Autoimmune HCV recurrence

Recurrent chronic HCV can present with plasma cell-rich, interface necroinflammatory activity resembling autoimmune hepatitis.²⁸ Determining whether this presentation represents an "autoimmune" variant of HCV, acute cellular rejection, *de novo* autoimmune hepatitis, or a combination is often very difficult and requires extensive history and evaluation. This recurrence variant is often recognized during the transition from acute hepatitis to chronic hepatitis or after the onset of chronic hepatitis. Typical histologic findings include "sheets of plasma cells" at the sites of severe interface and/or perivenular necroinflammatory activity.²⁹ In clinical scenarios where histology is highly consistent with autoimmune hepatitis, immunosuppressive therapy can be used to abrogate the severity of liver damage. However, such therapies may enhance HCV replication and promote HCV specific induced inflammation and fibrosis progression.

Factors affecting recurrence

Multiple factors are thought to affect HCV recurrence after liver transplant. These can be organized as traits of the host (recipient of new liver) or donor (transplanted liver) and viral factors.²³

Host factors

Gender

An epidemiologic study in the non-transplant setting demonstrated that females exhibit a slower rate of fibrosis progression per year and a lower overall incidence of end-stage liver disease than men.³⁰ Studies suggested a possible anti-fibrogenic effect of estrogen on hepatic stellate cells and less rapid progression pre-transplant.^{31,32} The situation appears to be different post-transplant; however, as one multicenter study of more than 500 HCV-positive recipients found the risk of severe hepatitis C recurrence following transplantation from a donor older than 60 years was doubled in female recipients compared to males.³³ Higher rates of graft loss and advanced fibrosis in women have been corroborated by a more recent study.³⁴

Host immune responses

Strong multispecific CD4+ and CD8+ T-cell responses are associated with spontaneous clearance and successful antiviral therapy during the course of HCV infection in the native liver—signifying their importance in abrogation of inflammation/fibrosis progression. The blunting of these seemingly protective adaptive immune responses by immunosuppression may actually contribute to the universal reinfection and accelerated disease progression observed after transplantation.³⁵ Detection of vigorous multispecific CD4+ T-cell responses in the early post-transplant period may predict mild graft injury and a greater response to antiviral therapy. The presence of strong innate immune responses (natural killer T cells) prior to transplantation may also

provide protection from severe graft injury following liver transplantation.³⁶

In addition to the aforementioned risks, older age, African American ethnicity, presence of metabolic syndrome, and coinfection with HIV have been associated with worse outcomes.^{37,38} It is speculated that these co-factors likely modulate the natural history of recurrence and are well established negative predictors of response to interferon based antiviral therapy.³⁹

Donor issues

Donor/transplant surgery-related issues

Multiple donor-related issues affect the outcome of hepatitis C infection in the post-transplant setting. Worldwide, the shortage of organs has led to an increasing use of "extended criteria donors." Such donor grafts of reduced quality may be more sensitive to damaging events such as ischemia/reperfusion injury and recurrent hepatitis C.⁴⁰

Age and donation after cardiac death

In liver recipients with HCV, older donor age has emerged as an important factor influencing disease recurrence and progression.⁴¹ The mean age of donors has increased over the last several years.⁴² Donation after cardiac death (DCD) liver transplantation is associated with worse patient and graft survival than donation after brain death liver transplantation, with increased incidence of biliary and vascular complications in HCV recipients, especially with older donors.⁴³⁻⁴⁵

Steatosis

The role of donor steatosis and recurrence in HCV patients is controversial. Fibrosis evolution appears to be higher when graft steatosis is over 30%,⁴⁶ and steatosis over 30-45% in the donor liver is often avoided when HCV is the transplant indication.⁴⁷ Apart from sensitivity to ischemia/reperfusion injury and HCV induced inflammation, there may be an influence of steatosis on adaptive immune responses.⁴⁸

Cold ischemia time

Recently implemented "Share 35" protocols have increased regional sharing of liver allografts that in turn may increase cold ischemia times. Recipients of livers from donors aged 45 years or older and cold ischemia times more than 12 hours showed increased risk of graft failure compared with recipients of livers from donors younger than 45 years and cold ischemia less than 12 hours.⁴⁹

Live donor transplantation

Living donor liver transplantation (LDLT) is a rapidly evolving field with expanding utilization in the face of significant organ shortage. The Adult-to-Adult Live Donor Liver Transplant Cohort Study found that graft survival in HCV-positive LDLT recipients (once there was sufficient LDLT experience at a given center) was similar to that of deceased donor liver transplant (DDLT) recipients.⁵⁰ Additionally, studies using protocol liver biopsies to assess disease severity found no significant difference in the rate of fibrosis progression

between recipients of LDLT and DDLT within a 5 year follow-up periods.⁵¹

Donor/host IL28B

Genome-wide studies have demonstrated a strong association between allelic variations in the Interleukin-28 (IL28B) gene and response to HCV therapy with interferon. The precise mechanism through which the IL28B single nucleotide polymorphism (SNP) genotype influences response to antiviral treatment has not been fully characterized. IFN-lambda 3, the product of the IL28B gene, belongs to the type III interferon family and induces interferon-stimulated genes (ISGs), differentiation of dendritic cells, modulation of Th1 and Th2 immune responses, and inhibition of T-regulatory (Treg) cells that serve as a critical link between innate and adaptive immune responses to viral infection.⁵² In a recent study, recipients with a CC genotype (favorable response to interferon based antiviral therapy) have relatively slower histologic recurrence, with decreased alanine aminotransferase (ALT) levels and viral load when compared with non-CC genotypes. The opposite association is seen with donor CC genotype.⁵³

Viral factors

Viral load and genotype

Higher HCV RNA levels in both serum and liver at the time of transplantation are linked with increased risk of progression to cirrhosis, graft loss, and death.³⁵ There is some controversy regarding the relationship between viral genotype and severity of recurrence, as genotype 1b has been associated with more severe recurrent hepatitis C in some patient series but not in others.^{54,55}

Viral genomic heterogeneity (Quasispecies)

Quasispecies diversity increases with the duration of chronic HCV infection and may be most robust in end-stage liver disease. Following liver transplantation, diversity falls during the early period of intense immunosuppression and remains low in those cases with rapidly progressive cholestatic hepatitis C.⁵⁶ Diversity frequently increases in those who develop mild chronic hepatitis, reflecting increased selective pressure during maintenance immunosuppression.⁵⁷

Concomitant virus post transplant

Both cytomegalovirus (CMV) and human herpesvirus 6 (HHV 6) infection have been associated with increased progression of fibrosis during HCV reinfection after liver transplantation.⁵⁸ These relationships highlight the importance of CMV prophylaxis in transplant populations.⁵⁹

Peri-transplant management of HCV

Historical perspective

The goal of any effective antiviral therapy is eradication with minimal side effects. Historically, previous standard of care treatment with pegylated interferon (Peg-IFN) and ribavirin (RBV) contributed to a number of side effects and was largely ineffective with sustained virologic response (SVR) rates

varying from 7–30% in HCV genotype 1 patients and 44–50% in non 1 genotypes.⁶⁰ Major predictors of achieving SVR included: low pretreatment viral load, Child Turcotte Pugh (CTP) score class A (genotype 1 only), and completion of treatment.⁶¹ These early studies highlighted the risk of decompensation with interferon based therapy in those with advanced fibrosis and a particularly high risk for infection.⁶² Despite the significant incidence of adverse effects and relative lack of efficacy, attempts at treatment were made in an effort to “deliver the patient aviremic” to transplant to lessen the chance of recurrence post-operatively. Investigators further evaluated the strategy of a low accelerating dose regimen (LADR) in populations with advanced fibrosis prior to transplant to prevent recurrence.⁶³ Treatment using a LADR was initiated with Peg-IFN-alpha-2b (0.75 µg/kg/week) and RBV (600 mg/day). Dose escalations were then performed at weeks one (Peg-IFN 1.5 microg/kg/week and RBV 800 mg/day), two (RBV 1.0 g/day), and three (RBV 1.2 g/day for patients weighing greater than 75 kg) based on tolerance, side effects, and weekly serum labs. Pre-transplant treatment prevented post-transplant recurrence of HCV infection in 25% of transplanted cases—22% in HCV genotypes 1/4/6 and 29% in HCV genotypes 2/3. The strongest predictor of post-transplant virologic response (pTVR) was duration of treatment prior to transplant; however, Peg-IFN and RBV were poorly tolerated with an increase in serious adverse events (cytopenias, infection, and hepatic decompensation) in the LADR treated cohort.

Directing acting antivirals pre-transplant

With the introduction of first generation direct acting antivirals telaprevir and boceprevir (NS3/4A protease inhibitors) in 2011, much interest focused upon their applicability in treatment experienced populations with advanced fibrosis. However, phase III studies did not include a large number of cirrhotics.^{64,65} Recently, results from the Compassionate Use of Protease Inhibitors in Viral C Cirrhosis (CUPIC) cohort evaluating the effectiveness of first generation protease inhibitor with Peg-IFN and RBV in treatment experienced HCV genotype 1 patients with cirrhosis were reported.⁶⁶ In 511 patients who did not respond to a prior course of Peg-IFN and RBV, telaprevir (n = 299) or boceprevir (n = 212) was used for 48 weeks. Among the telaprevir treated cohort, 74.2% of previous relapsers, 40.0% of partial responders, and 19.4% of null responders achieved SVR12. Among the boceprevir cohort, 53.9% of relapsers, 38.3% of partial responders, and none of the null responders achieved SVR12. While efficacy was certainly improved with addition of a first generation protease inhibitor, issues of tolerability remained. Severe adverse events occurred in 49.9% of cases, including liver decompensation and death in 2.2%. On multivariate analysis, baseline parameters, including prior null response and serum albumin level < 35 g/L, and platelet count ≤ 100,000, predicted serious adverse events and use was cautioned in patients with these factors.

Towards the end of 2013, two additional agents were added to the HCV armamentarium: simeprevir, a second generation once daily NS3/4A inhibitor, and sofosbuvir, an NS5B polymerase inhibitor of HCV.^{67,68} Clinical studies that led to Food and Drug Administration (FDA) approval for sofosbuvir demonstrated relatively high efficacy and safety in patients with cirrhosis.⁶⁹ Both agents are approved as agents in combination with either Peg-IFN or RBV. As previously

mentioned, there has been a rise in transplant listings for HCC related to HCV cirrhosis, and HCC may develop in those with well compensated cirrhosis (i.e., low native Model for End-Stage Liver Disease (MELD)). Such a patient population with relatively well compensated cirrhosis listed for orthotopic liver transplant by virtue of concomitant HCC represented an excellent opportunity to evaluate second generation DAA efficacy prior to transplant in preventing post-transplant recurrence. Curry *et al.* recently reported results from a Phase 2, open-label study investigating use of sofosbuvir plus RBV for up to 48 weeks in patients with HCV listed for liver transplant with HCC.⁷⁰ Patients with chronic HCV infection of any genotype listed for liver transplantation for HCC received up to 48 weeks of sofosbuvir (400 mg/day) and RBV (1000–1200 mg/day) before transplantation. Overall, sofosbuvir and RBV therapy was safe with well compensated cirrhosis and prevented post-transplant HCV recurrence in 64% of patients who had HCV RNA < 25 IU/mL prior to transplant. The number of consecutive days with HCV RNA target not detected prior to transplant appeared to be the strongest predictor of post-transplant HCV recurrence. Certainly, as new agents are developed, their applicability will be tested in cirrhotic populations to further optimize efficacy and minimize serious adverse events (Table 1).

Treatment of recurrence post-transplant

Given the difficulty in treating cirrhotic populations prior to transplant, much attention has focused on treatment post-transplant. In this context, two approaches have been examined: 1) a pre-emptive approach where antiviral therapy is used in the first weeks following transplantation and 2) a histologic, recurrence-based approach for patients with established hepatitis. Early post transplantation therapy administered during the first 2–7 weeks post-transplantation before there is clinical evidence of liver damage has been evaluated.⁷¹ The results have been disappointing overall in terms of antiviral efficacy and tolerability. With PegIFN based therapy, SVR rates of about 20% have been documented, ranging from 18 to 39% (5–33% in genotype 1 and 14–100% in genotypes 2/3).⁷¹ About 30% of patients discontinue treatment, and dose reductions are required in 70% secondary to side effects, such as bacterial infections, hematological toxicity, and rejections (0–26%).⁷²

The most widely used strategy involves the initiation of antiviral therapy once histologic consequences of HCV recurrence are detected on allograft biopsy. With PEG-IFN and RBV, the previous standard of care, studies estimate SVR at a rate of 30%.^{73,74} Transplanted patients were particularly predisposed to hematologic toxicities, especially anemia (60–80%), necessitating careful and frequent RBV dose adjustments.

In addition, patients with recurrent HCV infection treated with Peg-IFN (PEG) after liver transplantation can develop severe immune-mediated graft dysfunction (IGD) characterized by plasma cell hepatitis or rejection. A recent multicenter case-control study of 52 liver transplant recipients with hepatitis C assessed the incidence of, risk factors for, and outcomes of PEG-IGD.⁷⁵ Overall incidence of PEG-IGD during a 10-year study period was 7.2%. Variables associated with increased mortality included acute rejection as the PEG-IGD sub-type and lack of a SVR. Variables associated with graft failure included a high level of alkaline phosphatase at PEG initiation and lack of a SVR.

Table 1. Summary of Treatment Trials Pre-Transplant: Recent studies have evaluated the effectiveness of pegylated interferon (Peg-IFN) and ribavirin (RBV) in conjunction with newer direct acting antiviral agents including: sofosbuvir (SOF), simeprevir (SMV) and ledipasvir (LED). Identification of increasingly tolerable regimens prior to transplant able to achieve high SVR12 or reliable post transplant virologic response (pTVR) are in development.

Study	Agents	Patients (n)	Virologic response (%) (SVR 12/pTVR)	Adverse events (%)	Influential predictors
Everson <i>et al.</i> , ⁶³ 2013	Peg-IFN alfa2b & RBV (with dose escalation)	59	22% GT 1 29% GT 2/3	68-Serious	Duration of treatment >16 weeks
Hezode <i>et al.</i> , ⁶⁶ 2014	Peg-IFN alfa 2b & RBV with Telaprevir or Boceprevir	511 299-Telaprevir 212-Boceprevir	SVR12/Agent/Previous history Telaprevir 74.2/relapsers 40/partial responders 19.4/null responders Boceprevir 53.9/relapsers 38.3/partial responders 0/null responders	49.9-Serious	Response to prior therapy Albumin <35 g/L Plts<100,000
Curry <i>et al.</i> , ⁷⁰ 2013	Sofosbuvir & RBV	61	64%	18-Serious	Number of days with HCV RNA below lower limit of detection
Lawitz <i>et al.</i> , ⁸⁴ 2014	Simeprevir & Sofosbuvir +/- RBV	87	SVR12/Duration/Agent 93/12 weeks/SOF + SMV 93/12 weeks/SOF + SMV + RBV 100/24 weeks SOF + SMV 93/24 weeks/SOF +SMV + RBV	4.6-Serious	? Q80K polymorphism
Afdahl <i>et al.</i> , ⁸⁵ 2014	Ledipasvir & Sofosbuvir +/- RBV	440 total treated (88 Cirrhotic)	SVR12/Duration/Agent 86/12 weeks/SOF + LED 82/12 weeks/SOF + LED + RBV 99/24 weeks SOF + LED 99/24 weeks/SOF + LED + RBV	0-Serious 67-90% mild to moderate depending on regimen/duration	? NS5A resistance at baseline

Directing antivirals post-transplant

Interferon based therapy post-transplantation is fraught with a number of issues, including: comparative lack of efficacy, infection, anemia, and immune mediated graft dysfunction. However, similar to the case of their applicability immediately prior to transplant, much interest has focused on their efficacy in treatment of recurrence. A major limitation with first generation DAAs (telaprevir and boceprevir) are interactions with calcineurin inhibitors cyclosporine (CsA) and tacrolimus (Tac), the cornerstones of immunosuppression post liver transplant. Boceprevir and telaprevir are potent inhibitors of cytochrome P450 3A4. In a study of healthy volunteers, boceprevir was shown to increase the area under the curve of CsA and Tac by 2.7 and of 17, respectively.⁷⁶ In another study, the concomitant administration of a calcineurin inhibitor with telaprevir in healthy volunteers increased CsA and Tac exposures approximately 4.6-fold and 70-fold, respectively.⁷⁷

Recently, interim results from Europe evaluating the efficacy of telaprevir in conjunction with Peg-IFN and RBV post-transplant have been presented.⁷⁸ Patients receiving calcineurin based immunosuppression (6 months to 10 years after LT), with fibrosis stage F0-F3, received telaprevir, Peg-IFN, and RBV for 12 weeks and Peg-IFN and RBV for an additional 36 weeks. The study included 74 post-transplant patients, and at week 12, 40 (80%) patients on tacrolimus and 21 (87.5%) on cyclosporine achieved undetectable HCV RNA. Common adverse events included anemia, pruritus, and

rash. These results show improved efficacy with first generation DAAs and, importantly, manageable levels of immunosuppression with close monitoring.

A US based retrospective cohort study of 81 patients with genotype 1 HCV treated with boceprevir (10%) or telaprevir (90%) plus Peg-IFN and RBV was performed with SVR12 as the primary endpoint.⁷⁹ The intent-to-treat SVR12 rate was 63% in this post-transplant cohort. Patients with extended rapid virologic response (undetectable HCV RNA at 4 and 12 weeks after starting boceprevir or telaprevir) had higher rates of SVR12 compared to all other patients (85% vs. 15%). Similar to the European study, adverse effects were common; 21% of patients experienced hemoglobin <8 g/dL, and 57% required blood transfusions during the first 16weeks. Twenty seven percent were hospitalized, and 9% died.

In another investigation of 37 liver recipients with advanced HCV recurrence (either ≥ F2 fibrosis [n=31] or fibrosing cholestatic hepatitis [n=6]) treated with Peg-IFN, RBV, and first generation DAA, SVR12 was observed in 20% (1/5) and 71% (5/7) of patients in telaprevir and boceprevir groups, respectively (p=0.24).⁸⁰ Treatment was discontinued in 16 patients (treatment failures (n=11), serious adverse events (n=5)).

Emerging data with second generation DAAs shows promise in the post-transplant population regarding efficacy and tolerability. Preliminary results presented at AASLD 2013 showed that in a population of transplant recipients with HCV recurrence (predominately genotype 1) treated with sofosbuvir (400 mg daily) along with RBV (400 mg daily) with dose

escalation based on hemoglobin, 77% of patients achieved SVR 4 and all patients demonstrated HCV RNA below the lower limit of detection 4 weeks after treatment.⁸¹ Treatment was well tolerated and no interactions with immunosuppressive agents were observed. In addition, recent data from the sofosbuvir compassionate use program for patients with severe recurrent hepatitis C, including fibrosing cholestatic hepatitis following liver transplantation, showed higher rates of SVR12 (62%) than standard therapies in this context, improved liver function tests, and improved clinical outcomes⁸² (Table 2).

Recently, the use of sofosbuvir and simeprevir in combination has been examined.⁸³ At EASL 2014: Cohort 2 of the COSMOS trial consisting of those with advanced fibrosis (F3-F4) showed overall SVR rates of over 90% with a 12 week regimen not containing RBV.⁸⁴ Phase III clinical studies evaluating the combination of sofosbuvir and simeprevir are currently underway.

In the upcoming months, further regimens will be added to the HCV armamentarium. It is expected that newer approved regimens with agents such as ledipasvir (NS5A inhibitor) will have sufficient data to make recommendations for usage in those with cirrhosis and possibly on the road to liver transplant.⁸⁵ In addition, studies for the aforementioned agents are being conducted in post-transplant populations. In another recent study of a regimen containing ABT-450/r/ABT-267 along with ABT-333 and RBV in liver transplant recipients with genotype 1 recurrence, 96% of patients achieved an SVR12 with 24 weeks of therapy.⁸⁶ An unprecedented number of treatment regimens are on the horizon.

The American Association for Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) have published recommendations regarding treatment of HCV recurrence in the allograft.⁸⁷ Here is a new recommended treatment option for treatment naïve patients with genotype 1 recurrence in the allograft includes: sofosbuvir (400 mg) plus simeprevir (150 mg), with or without RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated

to weight-based dose of 1,000 mg [<75 kg] to 1200 mg [>75 kg]), for 12 weeks to 24 weeks. Another alternate regimen for treatment naïve patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis, is as follows: sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [>75 kg]) with or without Peg-IFN (in the absence of contraindication to its use), for 24 weeks in patients with compensated allograft HCV genotype 1 infection. A recommended regimen for treatment-naïve patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis, is as follows: sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dosages) with consideration of the patient's creatinine clearance value and hemoglobin level for 24 weeks. These guidelines are dynamic and are expected to be revised as new agents become approved and clinical experience grows.

Conclusions

Chronic Hepatitis C remains the leading indication for liver transplantation, and recurrence post-transplantation is universal for those who enter the transplant period with viremia. Recurrence is characterized by an accelerated progression to fibrosis that is thought to be related to loss of viral control in the context of systemic immunosuppression. A number of donor, host, and viral characteristics influence the clinical manifestations of recurrence. Previous standard of care therapy with Peg-IFN in end-stage liver disease was limited by decompensation, infection, and post-transplant by anemia. Newer additions to the direct acting antiviral armamentarium have been introduced with increasing applicability in cirrhotic and post-transplant populations. Their timely use prior to transplant is expected to improve outcomes post-transplant; and their use post-transplant is expected to improve morbidity and mortality.

Table 2. Summary of Treatment Trials Post-Transplant: Recent studies have evaluated the effectiveness of pegylated interferon (Peg-IFN) and ribavirin (RBV) in conjunction with newer direct acting antiviral agents including post-transplant

Study	Agents	Patients (n)	SVR 12 (%) (n where applicable)	Adverse events
Forns <i>et al.</i> , ⁷⁸ 2014 (interim analysis)	Peg-IFN alfa 2b & RBV & Telaprevir	74	59.6% (19/32)	11%-serious 60%-anemia
Burton <i>et al.</i> , ⁷⁹ 2014	Peg-IFN alfa 2b & RBV & Telaprevir or Boceprevir	81 (10% boceprevir/ 90%telaprevir)	63%	Common 21% Hgb<8g/dL 57% requiring transfusions 9% liver related death
Coilly <i>et al.</i> , ⁸⁰ 2014	Peg-IFN alfa 2b & RBV & Telaprevir or Boceprevir	37 Boceprevir (n=18) Telaprevir (n=19)	71% (5/7) Boceprevir 20% (1/5) Telaprevir	Common 16 discontinuations 92%-anemia
Charlton <i>et al.</i> , ⁸¹ 2013 (abstract)	Sofosbuvir & RBV	40	SVR 4-77%	15%-serious
Forns <i>et al.</i> , ⁸² 2014 (abstract)	Sofosbuvir & RBV	104	62%	48%-serious
Kwo <i>et al.</i> , ⁸⁶ 2014 (abstract)	ABT-450/r/ABT-267 + ABT-333 + Ribavirin	34	96.2%	5.8%-serious 17.6%-anemia

Conflict of interest

Dr. Seetharam reports the following: speaker’s bureau: Merck, Gilead; advisory boards: Janssen, Gilead.

Author contributions

Writing the review (BK, AS).

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