Published in final edited form as:

Curr Hepat Rep. 2011 September ; 10(3): 179–185. doi:10.1007/s11901-011-0103-5.

New and Evolving Management Paradigms for Hepatitis C after Liver Transplantation

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Abstract

Hepatitis-C induced liver failure is the leading indication for liver transplantation in the United States, and the burden of hepatitis C virus (HCV)-induced liver disease is not expected to peak for at least another decade. 2011 will usher in a new era of directly acting antiviral therapies and personalized medicine that will assist patients and clinicians in choosing the best drug regimen. Specific markers to predict sustained virologic response (SVR) in the posttransplant setting are under development, and the role of graft genetic markers like interleukin-28B and interferon- γ inducible protein-10 have yet to be fully defined. Lessons and experiences from treating the pretransplant population will be applied to patients with recurrent posttransplant HCV while studies specific to this population proceed. New paradigms for HCV treatment give promise to reducing the pretransplant burden of disease and improving SVR rates in the posttransplant population.

Keywords

Hepatitis C; HCV; Liver transplantation; Treatment; Therapy

Introduction

Currently, hepatitis C virus (HCV)-related liver failure remains the most common indication for liver transplantation in the United States [1] and in many North American transplant centers, the majority of liver transplants are performed for HCV-induced end stage liver disease (ESLD). The burden of HCV as the causative factor for cirrhosis, ESLD and hepatocellular carcinoma (HCC) is not expected to peak until 2020–2033 [2•] and thus, HCV can be expected to remain a prominent indication for liver transplant. Unfortunately,

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Disclosure A.S. Barritt has received honoraria from Salix Pharmaceuticals; J. Darling is a board member of Vertex and has received payment for development of educational presentations from Genetech and Gilead; P. Hayashi reported no potential conflicts of interest related to this article.

HCV infection will recur in 100% of liver transplant recipients if they have not attained a pretransplant sustained virologic response (SVR) [3, 4]. The natural history of HCV in the transplanted graft may be far more aggressive than HCV infections in native livers [5], and the complications of recurrent HCV in the transplanted graft include an increased incidence of graft loss, and increased mortality [5]. The aggressive posttransplant course of HCV may be predicted by donor and recipient factors, and is complicated by strategies for immunosuppression. Frequent comorbidities like anemia and renal dysfunction make HCV treatment after transplant challenging to the point the SVR rates are quite low, ranging from 24% to 27% in the posttransplant population [6]. New therapies for HCV in the pretransplant population may lessen the burden of posttransplant disease as well as make posttransplant SVR easier to attain, but the promise of new drugs and strategies for therapy has yet to play out in clinical practice.

Methods

In order to update the reader on new data germane to HCV therapy after liver transplantation, we searched the PubMed database during December 2010–February 2011 for English language manuscripts from the past year using the terms “Hepatitis C therapy,” “HCV therapy,” and “Liver transplantation.” A MESH (medical subject headings) search was performed using the above terms as well. Reference sections of selected manuscripts were searched for additional articles and electronic resources were used to find abstracts presented at major international meetings.

Evolving Treatment Strategies in the Pretransplant Patient

While the main focus of this review is HCV in the posttransplant patient, evolving approaches to treatment in the pretransplant patient cannot be ignored, as many, if not all, of the posttransplant approaches to therapy are predicated on pretransplant experiences.

Among the new approaches to treatment for HCV in 2011 will be the utilization of directly acting antiviral agents (DAA) for genotype 1 disease. First among this new class will be boceprvir (Merck, Whitehouse Station, NJ) and telaprevir (Vertex, Cambridge, MA). These agents promise to increase SVR rates into approximately the 60% to 70% range for patients with genotype 1 HCV [7•, 8•]. Trials for the use of these agents in posttransplant patients are ongoing. The efficacy of these new drugs in clinical trials may not translate into clinical effectiveness [9••], however, in regard to significantly reducing the burden of disease in the posttransplant population. Unless there is wider application of these new agents in the pretransplant setting, the prevalence of HCV cirrhosis and its complications will continue to increase [2••] and the posttransplant burden of HCV along with it. Additional challenges to using these new DAAs in the posttransplant setting include drug-drug interactions and the metabolism of both protease inhibitors and calcinurin inhibitors through the graft’s CYP3A system.

While the evolution of new clinical agents to treat HCV is critical, choosing which patients are appropriate for and have the best chance of SVR with treatment is equally important. Again, cues may be taken from the pretransplant population. Ge and colleagues [10••] found that the CC genotype of the polymorphism upstream from the IL28B gene is predictive of SVR across all races. The frequency of the CC genotype is far more common among people of European ancestry, accounting for approximately half of the difference in response rates between African Americans and people of European ancestry. Interferon- γ inducible protein-10 (IP-10) is a serum marker shown to predict SVR in both African Americans and Caucasians undergoing standard therapy for HCV. When IP-10 levels are combined with the IL28B genotype, the predictive ability for SVR becomes even more powerful, especially

among CT heterozygotes and TT homozygotes [11•]. The predictive value of these markers has not been prospectively validated in the posttransplant population or in combination with DAAs, but such tests may be a useful tool in determining which patients may be good candidates for therapy. In regard to predicting SVR in the transplanted graft, it remains unclear what role graft IL28 B and IP-10 may play, but the potential for pairing grafts with recipients by genetic markers that determine SVR rates remains a tantalizing opportunity to improve patient and graft survival in recurrent posttransplant HCV infection. This strategy has been proposed by Charlton, et al., [12•] who retrospectively examined donor and recipient IL28B genotypes in 189 patients transplanted for HCV liver failure between 1995 and 2005. They found that the TT genotype was associated with rapid progression of fibrosis and donor and recipient genotypes were each independently associated with SVR (Table 1).

Over the years, ribavirin has proven its value by decreasing the viral relapse rate including its necessity in combination therapy with DAAs. However, the side effect of hemolytic anemia can be severe for many patients and is dose limiting in up to 15% in the pretransplant population. While a drop in hemoglobin by week four was found to be predictive of significant anemia on treatment [13], until recently there were no pretreatment predictors of ribavirin induced anemia. Inosine triphosphatase (ITP) deficiency, considered previously a trivial condition, has been found to be protective against ribavirin induced hemolytic anemia and decrease the need for ribavirin dose reduction [14, 15]. While the mechanism of ribavirin induced hemolytic anemia is poorly understood, an accumulation of ITP within red blood cells may compete with ribavirin-triphosphate in the deleterious action ribavirin metabolites take on red cell membranes [14]. Posttransplant patients often have some degree of renal insufficiency which contributes to ribavirin toxicity, so establishing the role of ITP testing in this population may be particularly useful. Strategies for anemia management will increase in importance with the availability of protease inhibitors in 2011 which both carry a risk of significant anemia additive with the known ribavirin risk.

New findings specific to predicting SVR in the posttransplant population have recently been published by Fukuhara et al. [17]. In 50 patients with recurrent genotype 1b HCV who underwent interferon and ribavirin based therapy after living donor liver transplantation in Japan, 22 achieved SVR. The predictive potential of HCV viral mutations at amino acid 70 and 91 in the core region, mutations in the interferon sensitivity determining region and mutations in the interferon/ribavirin resistance determining region were found to be significant. Patients with double-wild type (DW) genotypes were thought to be more interferon sensitive. There was a stepwise increase in the rate of SVR with increasing number of wild type viral characteristics (Table 2) [16].

The ability to better predict outcomes to therapy and identify which patients may have side effects in combination with new therapies is ushering in a new era of personalized therapy for treating HCV in the pretransplant population. Many of these themes may be applied to treating HCV in the posttransplant setting.

HCV in the Allograft

A patient who enters into liver transplantation with a detectable viral load will have a recurrent HCV infection in the transplanted graft. While there have been reports of delivering interferon during the anhepatic phase of liver transplantation [17, 18], there have been no effective measures to prophylax against HCV transmission or reduced infection rates. Viral loads are reduced during the anhepatic phase of liver transplant, but quickly rebound as the graft is infected from circulating virions [19]. Within a few weeks, the HCV viral load will rebound to equal, or even exceed, the pretransplant viral load. Approximately

70% of posttransplant patients will progress to developing a chronic hepatitis, which often becomes apparent as an acute flair between 2 and 6 months after transplant [19].

When clinically significant HCV returns, as well as its severity, depends on several donor and recipient factors. Advanced donor age, increased cold ischemia time, and increased immunosuppression, especially bolus steroids or antibody therapy for acute rejection, have been found to lead to more severe recurrence of HCV in the allograft [5, 20]. Of note, the use of tacrolimus versus cyclosporine does not have an impact on HCV recurrence or its severity, [21] in spite of the perceived antiviral properties of cyclosporine. Recipients with high viral loads at the time of transplant and in the peri-transplant period are at increased risk of severe disease and HCV-related liver failure posttransplant, [22] as are those with stage 2 or higher fibrosis on liver biopsy during the first year after transplant [23].

Other viral infections in the posttransplant period predispose HCV infected patients to more severe recurrent disease. Cytomegalovirus (CMV) suppresses cell mediated immunity and posttransplant patients with HCV and CMV viremia are more likely to develop periportal/bridging necrosis [24]. Prophylaxis against CMV is recommended in high-risk patients and the relationship with severe recurrence of HCV with CMV viremia underscores the importance of this strategy.

The most severe form of recurrent HCV in the allograft is fibrosing cholestatic hepatitis (FCH) and affects 2% to 9% of patients transplanted for HCV [25]. In a systematic review of clinical and pathological findings in post liver transplant cholestatic hepatitis C, Narang et al. [25] found that the definition and method of diagnosis varied considerably in the literature. Additionally, reporting of risk factors and pertinent clinical data was not uniform, in spite of the consensus diagnostic criteria published in 2003 [26]. The heterogeneity of reporting and the relative rarity of FCH has made accurate data collection all the more difficult. Most agree, however, that patient mortality and graft loss with this entity is increased, and predicting which patients will be at greatest risk for FCH has been problematic. It is important to recognize the early features of FCH on biopsy as this may be the only time to intervene prior to graft loss. A novel sinusoidal fibrosis and cholestasis scoring system was recently proposed to aid in the early diagnosis of this entity [27]. Onset of FCH has been used as an indication for treatment, but SVR rates have been dismally low. Typically, the best outcome one can possibly obtain is viral suppression and stabilization of the graft with anti-viral therapy; some even recommending an indefinite duration of interferon [28].

Treatment Strategies: Pretransplant, Posttransplant Preemptive, Protocol–Biopsy Driven Therapy

The three main paradigms for treatment of patients with advanced hepatitis C disease are treatment prior to transplant, universal treatment after transplant, or treatment under certain clinical conditions after transplant. These strategies have been debated in multiple reviews [29–33] and are briefly summarized in Fig. 1. Many patients, even those with cirrhosis, or carefully selected patients with decompensated disease can be treated prior to liver transplant [34]. The benefit is that if a patient achieves an SVR, then the risk of posttransplant HCV recurrence will be removed. In some cases, such SVR may even lead to stabilization of liver function and portal hypertension, obviating the need for transplant. Difficulties in treating patients with cirrhosis include reduced tolerance of cytopenias, especially in the hypersplenic patient who already suffers from neutropenia, anemia and thrombocytopenia. Renal dysfunction such as Type II hepatorenal syndrome can decrease ribavirin clearance and increase the risk of anemia. Such complications can precipitate acute decompensation and even death prior to a graft becoming available. In general, patients with

a Model for End-Stage Liver Disease (MELD) score greater than 12–13 and/or Childs-Pugh greater than 7 should not be treated with standard therapy prior to transplant. However, the DAAs may allow patients with slightly higher MELD or Childs-Pugh scores to be treated, particularly if duration of treatment can be shortened to 24 weeks.

Universal therapy for all patients transplanted for HCV is appealing since HCV will universally recur in these patients, and treatment while the viral load is low could theoretically improve SVR rates. However, many if not most patients in the immediate posttransplant period are sufficiently frail, so that they may not tolerate interferon and ribavirin based therapies. A summary of studies implementing this strategy showed SVR rates in the 5% to 8% range [30]. Moreover, pegylated interferon has been associated with graft rejection and immediate treatment coincides with the period of highest risk of acute rejection.

The strategy most commonly employed after transplant involves delaying therapy until there is “clinically significant disease,” defined as stage 2 fibrosis by most practitioners and/or severe histologic activity, grade 3 or more. This strategy reserves therapy for those with active and scarring disease, rather than solely HCV viremia. On the other hand, delaying treatment may make SVR harder to achieve and may not be of benefit to those who develop early FCH. New fuel for the debate was provided in 2010.

Saab et al. [35•], performed a decision analysis model using Markov chain models for four treatment possibilities: no treatment, treatment of compensated cirrhotics prior to transplant, treatment of decompensated cirrhotics prior to transplant and treatment based on protocol biopsies after transplant. Compared to no therapy, treatment of patients with compensated cirrhosis increased quality adjusted life years (QALYs) and saved \$55,314. This strategy was superior to the alternates by Markov analysis. The authors also found that treating these patients resulted in 199 fewer deaths, 54 fewer HCCs and 66 fewer transplants than the no treatment strategy [35•]. These results are not terribly surprising, as it would be most clinicians’ preference to treat patients prior to decompensation of their liver disease, however, what should not be lost is that treatment of *decompensated disease* and treatment *after transplant* still provided an increase in QALYs and incremental cost savings compared to no treatment at all. As illustrated in the editorial by Rubin and Berenger [36], while the cost savings and QALYs of treating patients posttransplant was inferior to treating decompensated patients in the Markov model, the attributed costs of posttransplant care were inflated by growth factor use and protocol biopsies that may not be necessary in all patients. Furthermore, the reality is that most clinicians would likely prefer to treat stable transplant recipients than decompensated cirrhotics [36].

Most authors recommend 48 weeks of interferon and ribavirin therapy, regardless of genotype, for patients with recurrent HCV after liver transplant [31, 32]. The lessons learned from the pretransplant population, ie shorter duration of therapy for genotype 2 and 3 patients or genotype 1 patients with an RVR have not been fully vetted in the posttransplant population. Likewise, extending therapy to 72 weeks in slow responders has not been studied systematically either. The strategy of indefinite interferon therapy for those with FCH or severe disease as previously discussed is based on small case series and expert opinion. These paradigms will be challenged with the incorporation of DAAs into the posttransplant regimen.

Assessment of Hepatitis C Recurrence and Disease Severity

Historically, assessment of the severity of recurrent HCV and differentiating HCV from rejection has been achieved via liver biopsy. Liver biopsy is limited, however, by sampling error and significant inter observer variability. Nevertheless, liver biopsy remains the gold

standard for following the progression of fibrosis in the transplanted graft. The development of a non invasive method of assessing fibrosis in liver disease is hampered by comparing new modalities to this flawed gold standard [37], yet there has been progress.

HCV recurrence is exacerbated by immunosuppression induced impairment of cellular immunity. CD4+ adenosine triphosphate (ATP) release assays in blood correlates with global cellular immune function, and may help discern rejection from recurrent hepatitis C. While the level of accuracy has not been high enough to make the test widely used in clinical practice, there are some recent data that the assay may correlate with HCV-induced fibrosis. Alkhouri et al. [38], prospectively measured CD4+ ATP levels at four and 12 months posttransplant and compared their findings to protocol biopsies performed at the same time in 62 patients. They found that decreases in CD4+ ATP levels were significantly associated with increasing fibrosis scores [38]. CD4+ ATP levels may provide a non invasive means of assessing excessive immunosuppression that can lead to increased disease severity after transplant and help clinicians decide when to initiate posttransplant HCV therapy in the future.

Other alternatives to protocol liver biopsy have been evaluated recently. Benlloch et al. used a mathematical model, the Hospital Universitario La Fe (HULF) index, to estimate fibrosis in patients who had a liver transplant due to HCV infection. In this study, the authors prospectively validated and simplified a model first published in 2005 [39], and found that a formula using only the prothrombin time (PT) and aspartate aminotransferase (AST) reasonably predicted significant fibrosis (cirrhosis and bridging fibrosis) versus non significant fibrosis [40]. A drawback to this strategy, however, is that once the patient has developed significant fibrosis/cirrhosis, anti HCV therapy will be made all the more difficult for the posttransplant patient.

Manousou et al. [41], evaluated a quantitative histologic index using a digital image analysis of collagen proportionate area (CPA) from a liver biopsy slides. The biopsy specimens were obtained at 1 year posttransplant and stained with Sirius red in an attempt to predict the clinical outcome of patients transplanted for HCV. They found that the digital measurement of CPA was superior to both traditional Ishak staging and measurements of hepatic venous pressure gradients. Using a CPA cut off of 6% had 82% sensitivity and 95% specificity for decompensation. While CPA measurement may provide a more accurate qualitative and quantitative measurement of fibrosis, it does remain a technology based on invasive liver biopsy, and at best provides only an incremental advance in the assessment of disease severity.

Future Directions

The future for HCV patient and graft survival after transplant depends largely on how new pretransplant therapeutic modalities are integrated into medical practice, and how these modalities translate into the posttransplant setting. DAAs hold the promise to increase SVR rates into the 70% range in the pretransplant setting. However, it is unlikely such rates can be matched posttransplant. Immunosuppressive therapy will continue through treatment thus impairing both tolerability and the pegylated interferon portion of response. In the pretransplant setting, patients with inherent interferon resistance (eg IL28B genotype TT) may continue to have problems posttransplant achieving SVR if suboptimal responses or overt resistance to the protease inhibitors develop. Likewise, the safety and efficacy of these medications in the posttransplant setting, specifically the possibility of drug-drug interactions in the transplanted graft, are unknown. Nucleotide polymerase inhibitors with renal clearance and a different resistance profile may obviate the problem somewhat, but these remain in earlier phase trials.

The efficacy versus clinical effectiveness dilemma that besets the pretransplant HCV population may not be as germane to posttransplant HCV therapy. Patients who undergo liver transplantation are already highly selected for compliance and are likely treated at tertiary medical centers, thus their care may be more reflective of a clinical trial, and thus clinical effectiveness may better reflect efficacy rates reported in the literature. In any case, there is reason to believe that DAAs will eventually improve the relatively poor SVR rate for standard therapy posttransplant.

Genetic markers like IL28B, discovered using genome-wide association study methods predict sensitivity to interferon and ribavirin, and are important tools that can now be utilized in the pretransplant setting. For individual patients receiving genetically personalized therapy regimens pretransplant, the benefits will be dramatic and clear, particularly as DAAs come on line. From a community effectiveness point of view, the impact on posttransplant hepatitis C is less clear. If the higher rate of SVR with shorter duration of therapy spurs widespread screening and treatment of hepatitis C, then the number of patients coming to transplant could dramatically fall. Ironically, then the population of patients coming to transplant may be enriched with particularly difficult to treat patients due to unfavorable virus and/or host genetics.

The role that graft genotype plays, and the potential to match grafts and recipients to improve outcomes is unknown, yet holds promise for improved future outcomes. Prioritizing grafts with more treatable IL28 B genetics toward a hepatitis C patient ahead of a non-HCV patient with a higher MELD is unlikely to occur. However, grafts that are currently turned down for our hepatitis C patients due to older age or steatosis could become more acceptable if the genetics of the donor favor a higher chance of posttransplant treatment success. In other words, favorable graft genetics may make a marginal graft more acceptable and likely to be transplanted.

As we move into the era of DAAs, we will see improved antiviral response to therapy, but for now, interferon will remain the backbone of therapy. The long term goal for posttransplant HCV therapy will ultimately be to move away from interferon-based treatment. Interferon's immunomodulating effects make the specter of rejection omnipresent and patient tolerability of multidrug regimens is sure to improve in interferon's absence.

Conclusions

Treating HCV in the posttransplant setting in 2011 and beyond will include a more personalized approach to therapy. Recipient and possible graft genetic markers will be utilized to predict both SVR rates and potential side effects to therapy. New drugs, especially the emerging class of DAAs, hold the promise to increase pretransplant SVR rates, and if disseminated widely, will shrink the burden of posttransplant recurrent HCV. The role of DAAs in the posttransplant setting is not yet defined, but may abrogate feared complications like FCH and increase SVR rates while improving patient and graft survival. New methods for assessing fibrosis may render protocol liver biopsies obsolete and aid in the early detection of FCH. However, discerning rejection from recurrent hepatitis C clinically and histologically remains a problem without clear advances in sight. Lessons and experiences from treating the pretransplant population will continue to be applied to patients with recurrent posttransplant HCV while studies specific to this population are ongoing.

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Peri-transplant HCV Treatment Strategies

Fig. 1.
Peri-transplant HCV treatment strategies

Table 1

SVR rates for treatment of post transplant HCV by donor and recipient IL28B genotype

IL28B Genotype	n	SVR (%)	p
Donor (<i>n</i> -CC)	19	16	0.0095
Recipient (<i>n</i> -CC)			
Donor (CC)	22	50	
Recipient (<i>n</i> -CC)			
Donor (<i>n</i> -CC)	12	42	
Recipient (CC)			
Donor (CC)	7	86	
Recipient (CC)			

CC CC genotype for IL28B, *n*-CC genotypes other than CC (CT or TT) for IL28B, *p* value for trend, SVR sustained virologic response; Adapted from Charlton, et al. [12•]

Table 2

Interferon sensitivity score according to hepatitis C viral factors

Interferon sensitivity score	n	SVR (%)	p
0	17	17.6	<0.001
1	21	38.1	
2	7	85.7	
3	5	100	

P value for trend, *SVR* sustained virologic response; Interferon sensitivity score calculated by the presence of three factors: 1) double wild type at amino acid 70 and 91; 2) interferon sensitivity determining region ≥ 2 ; and 3) interferon/ribavirin resistance determining region ≥ 6 . Adapted from Fukahara, et al. [16]