Hepatitis C-associated liver failure is the most common indication for liver transplantation, with virological recurrence near ubiquitous. Approximately 30% of HCV-infected recipients will die or lose their allograft or develop cirrhosis secondary to hepatitis C recurrence by the fifth postoperative year, with the proportion increasing with duration of follow-up. Strategies for minimizing the frequency of severe HCV recurrence include avoidance of older donors, early diagnosis/treatment of CMV and minimization of immunosuppression, particularly T-cell depleting therapies and pulsed corticosteroid treatment of acute cellular rejection. Patients should be offered treatment with peginterferon and ribavirin before LT if MELD \( \leq 17 \) or as soon as histological evidence of recurrence of HCV is apparent post-LT. Because of the high frequency of hemotoxicity and renal insufficiency, ribavirin should be dosed according to renal function.

Key words: HCV, immunosuppression, liver transplantation, recurrence, treatment

Abbreviations: HCV, hepatitis C virus; NIDDK, National Institutes of Digestive Diseases and Kidney.

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Introduction

Although possibly having peaked in 2002 in the United States (http://www.ustransplant.org/), hepatitis C virus (HCV)-associated liver disease continues to be the most common indication for liver transplantation (LT). Although the impact of HCV infection varies substantially between recipients, allograft failure secondary to recurrence of HCV infection is the most frequent cause of death and graft failure in HCV-infected recipients. This review provides a practical analysis of our current understanding of HCV infection in the liver transplant recipient, with a focus on managing immunosuppression, timing and dose of antiviral treatments as well as donor and recipient factors that may affect outcomes.

Posttransplant Course of HCV Infection

HCV infection of the allograft occurs at the time of transplantation, with negative-strand HCV RNA detectable in the first postoperative week. HCV RNA is cleared rapidly from serum during the anhepatic phase. Following reperfusion, the rate of decrease in HCV RNA accelerates, almost certainly reflecting HCV binding to its obligatory hepatic receptors. HCV RNA levels typically increase rapidly from week 2 posttransplantation, peaking by the fourth postoperative month. At the end of the first postoperative year, HCV RNA levels are, on an average, 10–20-fold greater than pretransplant levels (1). Histological features of hepatitis develop in approximately 75% of recipients in the first 6 months following LT (2). By the fifth postoperative year up to 30% have progressed to cirrhosis (2). A small proportion of patients (4–7%), develop an accelerated course of liver injury (cholestatic hepatitis C, associated with very high levels of viremia) with subsequent rapid allograft failure. Early post-LT histology, for example at 1 year, has been consistently predictive of subsequent fibrosis progression (1) (Figure 1).

The impact of recurrence of HCV on the allograft has led to long-term graft survival for recipients with HCV infection that is relatively lower than that of recipients undergoing liver transplantation for most other indications (3). In the absence of any serious debate concerning whether or not patients with HCV infection should have access to LT, it is important to understand the interplay of factors that can affect the course of outcomes following LT for HCV-associated liver disease.

Immunosuppression—Impact on Viremia and Recurrence

Corticosteroids

Pulsed intravenous methylprednisolone treatment for acute cellular rejection is associated with transient 1–2 log increases in HCV RNA levels (4). In addition to being proviral, treatment of acute cellular rejection with corticosteroids is associated with increased mortality and graft loss.
in LT recipients with HCV infection (relative risk = 2.7–2.9, p = 0.04) (5).

It has been suggested, though not proven, that a slow steroid taper is better than a rapid taper. Although steroid sparing regimens appear to be safe, a large (n = 312) randomized controlled study, that included a steroid free arm of immunosuppression, has, to date, found no difference in the rate of recurrence of HCV nor in patient or graft survival between steroid free and steroid utilizing arms (6). There is no compelling basis for avoiding corticosteroids in the early postoperative period.

**Calcineurin inhibitors**

In the nontransplant setting, cyclosporine A treatment does not produce changes in HCV viremia. Although no studies of the independent impact of tacrolimus on HCV viremia have been reported, posttransplant HCV levels are similar among patients receiving tacrolimus and patients receiving cyclosporine A.

The relative impact of the choice of calcineurin inhibitor on posttransplant outcomes merits detailed consideration. In a prospective randomized controlled study of 495 recipients with HCV infection, no difference was seen in the histological recurrence rate of hepatitis C at 12 months post-transplantation between patients receiving cyclosporine versus tacrolimus (7). A meta-analysis of studies comparing the two calcineurin inhibitors, however, found a patient and graft survival benefit associated with tacrolimus as maintenance immunosuppression (graft loss: hazards ratio [HR] = 0.73, 95% CI = 0.61–0.86) (8). There is emerging evidence that cyclosporine may have an impact on HCV biology that requires concomitant administration of interferon. The binding of NS5B to cyclophilin B is inhibited by cyclosporine A (cyclophilin B is a functional regulator of the NS5B-RNA-dependent RNA polymerase). In the nontransplant setting, the combination of IFN-α and cyclosporine results in significantly higher virological and biochemical response rates than IFN-α monotherapy. The potentiation of the antiviral effects of cyclosporine was strongly implied in a study in which 21 liver transplant recipients with recurrence of HCV were treated for 6 months with peginterferon alpha and ribavirin while maintained on tacrolimus monotherapy for maintenance immunosuppression (9). Eight patients who had not achieved a virological response after 6 months of antiviral therapy were switched from tacrolimus to cyclosporine. Five of these eight became HCV RNA negative after the conversion from tacrolimus to cyclosporine. These intriguing data need to be confirmed in a controlled fashion. Further evidence of the importance of cyclophilin B inhibition in the treatment of HCV was demonstrated by the antiviral effects of a non-immunosuppressive, potent inhibitor of cyclophilin, Debio-025, in HCV/HIV coinfected patients (10). The availability of nonimmunosuppressive cyclophilin inhibitors is eagerly awaited in the transplant arena. Meanwhile, a theoretical case could be made for using tacrolimus as initial (e.g. for the first two postoperative months) maintenance immunosuppression for recipients with HCV infection, changing to cyclosporine during interferon-based antiviral therapy. Such an approach would take advantage of cyclophilin-inhibiting properties of cyclosporine during antiviral therapy and the greater immunosuppressive potency of tacrolimus for maintenance immunosuppression, minimizing the frequency of acute cellular rejection.

**Mycophenolate mofetil**

Mycophenolate mofetil (MMF), a potent inosine monophosphate inhibitor (as is ribavirin), has been shown to have antiviral properties against flaviviruses. Neither HCV RNA levels nor liver biochemistries are thought, however, to be affected significantly by MMF treatment. Although MMF has been reported to be associated with more severe recurrence of HCV, a negative impact of MMF on recurrence of HCV has been refuted by analyses of the UNOS/SRTR database (11) and large randomized controlled trials (12), which found MMF triple therapy was associated with a reduced risk of death (HR = 0.77, p < 0.001) and graft loss (HR = 0.81, p < 0.001) (11). Based on the aggregate of these reports, the impact of MMF on recurrence of HCV appears to be neutral or beneficial to long-term outcomes.

**T-cell depleting therapies**

OKT3 administration has consistently been identified as a significant risk factor for both the time to development of and the severity of histological recurrence of hepatitis C. The notion of a negative impact of T-cell depletion on posttransplant outcomes in recipients with HCV infection is supported by the potent effect of alemtuzumab (campath) in exacerbating recurrence of HCV (13). Data concerning the impact of rabbit antithymocyte globulin (ATG), an increasingly popular induction agent, are less clear. Outcomes in patients with HCV infection who received induction ATG have been reported to be similar to controls who
did not receive ATG, with an analysis of outcomes from three centers further suggesting that induction with ATG is associated with less severe fibrosis progression (14). The interpretability of any of these studies is greatly limited by the lack of protocol biopsies and the use of historical controls. While it is possible that the complex effects of ATG on the relative abundance of T- and B-cell subsets results in an immune milieu that favors less severe recurrence of HCV (in contrast to the specific CD3 depletion associated with OKT3), in the absence of data from randomized controlled studies, thymoglobulin should be used with caution, if at all, in liver transplant recipients with HCV infection.

**Interleukin-2 receptor inhibition**

Large (n = 300) randomized, controlled studies of Interleukin-2 receptor antibody-based therapy in liver transplant recipients with HCV infection suggest a neutral impact on medium-term outcomes, including allograft histology (6) (15).

**Impact of Donor and Recipient Risk Factors**

**Viral and recipient factors**

Although HCV genotype and quasispecies emergence have been variably reported to impact severity of recurrence of HCV, viral factors lack sufficient sensitivity and specificity to be used in determining eligibility of patients for liver transplantation or identifying candidates for preemptive antiviral therapy. The same holds true for recipient variables, including recipient age, gender, HLA type and ethnicity (16, Table 1).

**Donor factors**

Donor factors are potentially modifiable or selectable and are thus of particular interest. An association of advancing donor age with more rapid and severe histological progression of HCV recurrence has been very reproducible (16). The effect is nonlinear, with donor age greater than 65 years associated with more rapid progression of fibrosis and allograft failure. Prolonged cold and warm ischemia times have also been identified as risk factors for more severe post-LT HCV infection, as has early posttransplant preservation injury (17). Recurrence of HCV is not affected by the use of living-donor organs, when compared to deceased-donor organs, provided total center volume exceeds 20 (18).

**CMV**

Posttransplant CMV infection has been repeatedly and strongly associated with increased severity of recurrence, even after adjusting for covariables such as degree of immunosuppression (16). While these data suggest that targeted prophylaxis against CMV might reduce the impact of CMV infection on posttransplant outcomes in HCV-infected liver transplant recipients, a randomized controlled trial directly addressing this question has never been performed.

**Human immunodeficiency virus (HIV)**

Human immunodeficiency virus coinfection has recently emerged as an important predictor of poor survival among liver transplant recipients with HCV infection (19). One-year patient mortality attributable to HCV in coinfected recipients ranges between 27 and 54%. Factors associated with increased risk of post-LT mortality among HCV–HIV coinfected recipients include African-American recipient ethnicity, pre-LT MELD score of >20, intolerance of HAART therapy and higher pre-LT HCV level of viremia (19). Reduced response rates to treatment of HCV with interferon and ribavirin further attenuate post-LT outcomes in HIV–HCV coinfected liver transplant recipients. Strategies for improving outcomes in this fragile population are evolving.

**Antiviral Therapy**

Published studies describing antiviral therapy among recipients with HCV infection are difficult to compare due to the differences in the definition of recurrent hepatitis C, timing of initiation of anti-HCV therapy, choice of antiviral agents and doses as well as study end points. With these caveats in mind, a summary of insights gained from the studies reported to date follows.

**Pretransplant antiviral therapy**

Patients with higher preliver transplant HCV RNA titers experienced greater mortality and graft loss rates than recipients with lower pretransplant HCV RNA titers (20). Treatment, however, in high MELD score patients is poorly
The importance of early virological response (EVR, i.e. HCV avirin, reported an SVR of 33% with combination therapy. Late responses can also be associated with SVR. All other reports of peginterferon-based treatment of recurrence of HCV have been retrospective. More recent studies utilizing pegylated IFN-α for established recurrence have reported more favorable outcomes (Table 2). In aggregate, using standard dosing of peginterferon and ribavirin, approximately 50% ETR and 30–35% SVR can be expected with 48 weeks duration therapy for patients with genotype 1. The efficacy of pegylated interferon and ribavirin is thus approximately one-third less than in the nontransplant setting.

### Optimizing antiviral treatment
Factors contributing to the low response rates among liver transplant recipients include marrow suppression by interferon when used in combination with immunosuppressive drugs and poor tolerability of ribavirin. In a pooled analysis of 21 studies by using peginterferon and ribavirin for treatment of recurrent HCV, two-thirds of patients required dose reductions of either peginterferon or ribavirin and one-fourth discontinued treatment early (24). Factors associated with poor response are genotype 1, absence of early virological response, male gender, high baseline viral load and insulin resistance. As ribavirin levels are a major determinant of toxicity as well as efficacy, making dose adjustments of ribavirin according to levels would be desirable. Unfortunately, measurement of ribavirin levels is not available at most centers. As ribavirin is primarily renally excreted and has a half-life of approximately 300 h, the potential for dose-dependent toxicity is substantial in the posttransplant setting. Lower initial ribavirin dosing, increasing as tolerated, or dosing based on a nomogram that incorporates renal function (creatinine clearance) is highly recommended (Figure 2) (25). In the nontransplant setting, higher doses and longer duration of therapy can both increase SVR rates.

### Posttransplantation
#### Early prophylactic treatment
There are two randomized, controlled trials—a prophylaxis trial and a treatment trial—reporting the safety and efficacy of peginterferon alfa-2a in the early postoperative period (22). In the prophylaxis trial, treatment was initiated within 3 weeks after OLT versus 6–60 months in the treatment trial. Only two patients treated in the prophylaxis trial (8%) and three in the treatment trial (12%) achieved an SVR. A nonrandomized preemptive therapy study reported similar (5%) SVR rates. Thus, treatment in the early postoperative period is acceptably tolerable but of very poor efficacy.

#### Treatment of established recurrence
There are also only two randomized controlled trials of (peg)interferon and ribavirin treatment of recurrence of HCV (Table 2). The largest study, utilizing a mix of interferons, reported a 21% SVR (23). A smaller study, using peginterferon alfa +/− ribavirin, reported an SVR of 33% with combination therapy. The importance of early virological response (EVR, i.e. HCV RNA ≥ 2 log drop at week 12) on SVR was noted, with half of patients with EVR achieving an SVR versus none who had not achieved EVR. This almost certainly overstates the importance of EVR in the posttransplant setting, where late responses can also be associated with SVR. All other reports of peginterferon-based treatment of recurrence of HCV have been retrospective. More recent studies utilizing pegylated IFN-α for established recurrence have reported more favorable outcomes (Table 2). In aggregate, using standard dosing of peginterferon and ribavirin, approximately 50% ETR and 30–35% SVR can be expected with 48 weeks duration therapy for patients with genotype 1. The efficacy of pegylated interferon and ribavirin is thus approximately one-third less than in the nontransplant setting.

### IFN and the risk of rejection or immune hepatitis
The reported incidence of ACR on interferon-based antiviral therapy ranges from 0 to 25%, with a mean incidence of 12% (Table 2). The frequency and severity of ACR is typically not significantly greater than reported in patients

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**Table 2: Summary of larger pegylated interferon/ribavirin treatment studies**

<table>
<thead>
<tr>
<th>First author</th>
<th>n</th>
<th>PEG-IFN dose per week</th>
<th>Ribavirin dose (mg/day)</th>
<th>CT (%)</th>
<th>ACR (%)</th>
<th>ETR (%)</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mukherjee</td>
<td>39</td>
<td>Goal 1.5 μg/kg</td>
<td>Goal 800</td>
<td>46</td>
<td>0</td>
<td>67</td>
<td>31</td>
</tr>
<tr>
<td>Dumortier</td>
<td>20</td>
<td>0.5 → 1.0 μg/kg</td>
<td>400→1200</td>
<td>80</td>
<td>25</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>Rodriguez-Luna</td>
<td>19</td>
<td>0.5 → 1.5 μg/kg</td>
<td>400→1000</td>
<td>51</td>
<td>5</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>Ross</td>
<td>16</td>
<td>1.5 μg/kg</td>
<td>1200</td>
<td>75</td>
<td>0</td>
<td>38</td>
<td>18</td>
</tr>
<tr>
<td>Neff</td>
<td>57</td>
<td>1.5 μg/kg</td>
<td>400–600</td>
<td>68</td>
<td>0</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Castells</td>
<td>24</td>
<td>1.5 μg/kg</td>
<td>400–800</td>
<td>100</td>
<td>4</td>
<td>58</td>
<td>35</td>
</tr>
<tr>
<td>Fernandez</td>
<td>47</td>
<td>1.5 μg/kg</td>
<td>800–1000</td>
<td>79</td>
<td>6</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>Oton</td>
<td>55</td>
<td>1.5 or 180 μg</td>
<td>800–1200</td>
<td>70</td>
<td>0</td>
<td>67</td>
<td>44</td>
</tr>
<tr>
<td>Mukherjee</td>
<td>32</td>
<td>180 μg</td>
<td>1000–1200</td>
<td>66</td>
<td>6</td>
<td>50</td>
<td>41</td>
</tr>
<tr>
<td>Angelglico</td>
<td>21</td>
<td>180 μg</td>
<td>200–600</td>
<td>45</td>
<td>5</td>
<td>52</td>
<td>33</td>
</tr>
</tbody>
</table>

CT = completed therapy; ACR = acute cellular rejection; ETR = end-of-treatment response; SVR = sustained viral response at 6 months posttreatment.

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Ross converted interferon-treated patients to pegylated interferon during treatment.

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1 Ross converted interferon-treated patients to pegylated interferon during treatment.
Management of HCV Infection Following Liver Transplantation

Strategies for Minimising the Impact of Post-LT HCV Infection

<table>
<thead>
<tr>
<th>Pretransplant</th>
<th>Peritransplant</th>
<th>Early Post-LT (0-6 months)</th>
<th>Medium and Late Post-LT (&gt;6 months post-LT)</th>
<th>During Antiviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>If MELD &lt;17, consider antiviral therapy using low initial dosing</td>
<td>Avoid donors &gt;65 years</td>
<td>Consider CMV prophylaxis unless donor and recipient negative for CMV IgG</td>
<td>Consider protocol liver biopsies at every other yearly interval unless fibrosis stage &gt;/=3, regardless of biochemical profile.</td>
<td>Measure GFR and adjust ribavirin dosing for GFR: 20-39mls/mn =&gt; 200mg/day 40-59mls/mn =&gt; 400mg/day 60-79mls/mn =&gt; 600mg/day 80-99mls/mn =&gt; 800mg/day 100+ mls/mn =&gt; 1000mg/day</td>
</tr>
<tr>
<td>If MELD &gt;17, avoid antiviral therapy</td>
<td>Avoid T-cell depleting induction therapies</td>
<td>Avoid corticosteroid boluses for treatment of mild ACR (add MMF +/- increase CNI dosing instead)</td>
<td>Initiate antiviral therapy if histological evidence of recurrence of HCV</td>
<td>Consider change to CsA during antiviral therapy for effect of cyclophilin inhibition</td>
</tr>
<tr>
<td>Consider use of HCV RNA positive donors if no abnormal fibrosis</td>
<td>Avoid T-cell depleting treatments</td>
<td>Consider insulin sensitization if impaired glucose tolerance diagnosed</td>
<td>Consider 48 weeks of Rx regardless of genotype</td>
<td></td>
</tr>
<tr>
<td>Avoid prolonged warm ischemia times (&gt;90mins)</td>
<td>Use tacrolimus for maintenance CNI</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2: Potential strategies for minimizing the impact of HCV infection liver transplantation are shown. Recommendations with less strong evidence are shown as considerations. GFR-based dose adjustments are based on the nomogram developed by Maeda et al. (25).

with recurrence of HCV infection who are not receiving antiviral therapy (22).

Alloimmune hepatitis can occur in association with post-LT antiviral therapy in approximately 5% of cases, typically after HCV RNA clearance and associated with an important risk of graft failure (26). Immunosuppression levels decrease significantly in patients responding favorably to anti-HCV therapy, predisposing to ACR. Thus, although the risk of ACR is small, immunosuppression monitoring and maintenance are essential during treatment, with a low threshold for adjusting immunosuppression in the face of falling trough CNI levels or histological evidence of alloimmune hepatitis. Because of the potential for progressive allograft injury and graft loss, flaring of biochemical abnormalities on or after administration of antiviral therapy should prompt a detailed rapid evaluation. Liver biopsy should be considered early in this setting. Although there are no randomized controlled trials comparing treatment strategies of alloimmune hepatitis, success has been reported with increased dosing and mechanisms of immunosuppression (26,27).

**Impact of treatment on outcomes:** Studies in nontransplant patients have shown that treatment of chronic hepatitis C leads to an improvement in liver histology. Similarly, randomized controlled trials have reported improvement in fibrosis score in treated when compared to untreated liver transplant recipients with recurrence of HCV (23). In addition, a recently published analysis, conducted by the authors of this review, comparing, in a retrospective fashion, long-term outcomes among patients with recurrence of HCV post-LT found graft survival was significantly higher among patients who received antiviral treatment, regardless of SVR (28). Although further studies are needed to confirm the favorable impact of antiviral therapy on post-transplant outcomes, the preponderance of the available evidence suggests that treatment should be considered before more advanced (fibrosis stage ≥ 2) in the course of recurrence.


**Evolving Treatment Strategies**

Patients who are able to maintain higher doses of ribavirin have a reduced risk of virological relapse. Early initiation of erythropoietin is associated with less severe anemia and lower frequency of dose reductions of ribavirin. Similarly, granulocyte macrophage colony stimulating factor (GM-CSF) may be used to increase neutrophil counts. The thrombopoietin-receptor agonist eltrombopag has recently been shown to enhance platelet counts in a dose-dependent manner in patients undergoing antiviral treatment with peginterferon and ribavirin. None of the growth factors have been shown to increase SVR in the posttransplant setting.

Currently, there are many new direct antiviral agents, as well as a potentially less hemotoxic ribavirin prodrug, under investigation for the treatment of chronic HCV infection. While results of phase II trials with protease inhibitors and polymerase inhibitors have been promising, there are no data regarding their efficacy or safety in the transplant setting. All protease and polymerase inhibitors that are at or beyond phase 2 of clinical development require ribavirin and peginterferon for optimal efficacy. Once the first protease or polymerase inhibitors are approved for the treatment of chronic hepatitis C, trials may be designed to assess whether these drugs can be used to achieve an undetectable viral load before transplantation to avoid post-transplant HCV recurrence or to improve efficacy of post-transplant treatment.

**Summary and Conclusions**

HCV-associated liver failure continues to be the most common indication for liver transplantation, with virological recurrence near ubiquitous. Although outcomes for recipients with HCV infection are generally comparable to those for other indications for liver transplantation, the impact of HCV recurrence on posttransplant patient and graft survival is substantial. Approximately 30% of HCV-infected recipients will die or lose their allograft or develop cirrhosis secondary to hepatitis C recurrence by the fifth postoperative year, with the proportion increasing with duration of follow-up. Strategies for minimizing the frequency of severe HCV recurrence are evolving and include avoidance of older donors, early diagnosis/treatment of CMV and minimization of immunosuppression, particularly T-cell depleting therapies and pulsed corticosteroid treatment of acute cellular rejection. Competing goals of reducing immunosuppression and avoiding treatment of acute cellular rejection complicate the choice of immunosuppressive agents. Patients should be offered treatment with peginterferon and ribavirin as soon as histological evidence of recurrence of HCV is apparent. Because of the high frequency of hemotoxicity and renal insufficiency, ribavirin should be dosed according to renal function. Studying the role of HCV polymerase and protease inhibitors in the management of post-LT HCV infection, including drug–drug interaction studies, should be a high priority.

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