Hepatitis C virus recurrence after liver transplantation

Summary

Cirrhosis due to hepatitis C virus (HCV) is now the most common indication of liver transplantation in Western Europe and the United States. In the absence of effective prophylaxis, recurrent HCV infection is almost inevitable. Though the natural history and intermediate term outcome of recurrent HCV are now better documented, those factors which may influence the recurrence of hepatitis and consequent progression of graft disease remain unclear. Interferon (IFN) as a sole agent for the treatment of recurrent infection has proved unsatisfactory. Early intervention with a combination of IFN and ribavirin seems promising, and this approach may prevent or delay progression of HCV related graft disease after liver transplantation.

Introduction

Since the identification of hepatitis C virus (HCV) in 1989,1 it soon became evident that hepatitis C represents a major public health problem in Europe and in the United States. Chronic infection progresses to cirrhosis in at least 20% of patients, and liver failure will occur in more than 10% of infected patients after 20 years of carrying the virus.2 HCV infection is an established risk factor for hepatocellular carcinoma.3 Unfortunately, the results of interferon (IFN) treatment are disappointing, and a sustained response will be observed in fewer than 20% of patients treated.4 Hence, available treatment may have little impact on disease progression for the majority of patients, and HCV will become an increasingly important indication for liver transplantation. Already, 15–20% of European and North American transplant candidates are infected with HCV.5 1859 European patients have been transplanted for HCV associated cirrhosis since 1985.6

As a result of improved virus detection methods, progress has been made in the understanding of HCV recurrence after transplantation. For example, the development of advanced antibody tests has reduced the number of false positive results. More importantly the development of molecular biological techniques has permitted better appraisal of replication dynamics. The clinical manifestations of recurrent HCV are extremely variable, and range from total absence of symptoms with normal biochemistry to severe cholestasis hepatitis with rapid progression to cirrhosis. Our understanding of the pathogenic mechanisms which underlie this clinical diversity remains unsatisfactory. The management of recurrent infection and the use of antiviral therapy in the context of transplantation therefore remain a challenge.

In this review we discuss the diagnosis, natural history, pathogenesis, and treatment of HCV recurrence after liver transplantation.

Diagnosis of recurrent HCV infection

HCV infection of the liver transplant recipient represents acquired infection or recurrent infection, or both. Genetic sequencing of variable regions of the viral genome permits comparison of pre- and post-transplant HCV species, and distinguishes recurrent from acquired infection.7 Circulating virus, and virus harboured in extrahepatic sites, provides clues for the type of graft infection. For instance, peripheral blood mononuclear cells have been shown to contain negative strand viral RNA, the replicative intermediate of the viral genome.8

Initial studies relying on second generation serological assays underestimated the frequency of recurrent HCV infection. Among patients who are HCV positive before transplantation, the antibody seroprevalence after transplantation by first and second generation assays varied from 41 to 83%.9 10 Loss of antibody seropositivity is probably the consequence of immunosuppressive treatment. Poterucha et al confirmed the inferior sensitivity of serological tests, compared with PCR detection of viral RNA, for the diagnosis of recurrent HCV in the transplant setting.11 In fact, HCV RNA can be detected in most HCV RNA positive liver transplant recipients after transplantation.12 13 Viral RNA can be detected in serum and liver during the first post-transplant month.14

Reliable quantitation of viral RNA using techniques such as the branched chain DNA assay may also prove to be useful for the investigation of recurrent infection after transplantation. For instance, the lobular hepatitis observed after recurrent infection may be associated with an extremely high serum viral titre.15 Therefore, measurement of viral titres may permit the early diagnosis of recurrent hepatitis, and may influence subsequent patient management (including the early administration and subsequent adjustment of antiviral treatment).

More recently it has been suggested that the detection of IgM anti-HCV core may be a sensitive marker of viral recurrence, independent of the level of immunosuppression. Its measurement might provide early evidence of graft hepatitis.16

Natural history of HCV recurrence after transplantation

As transplanted patients now expect to survive long term, the management of recurrent HCV has assumed greater importance. Viraemia can exist in the absence of histological lesions17 and the HCV RNA titre may not reflect the histological changes. Recurrent infection is not necessarily associated with graft hepatitis, which may still be absent in as many as 50% of patients within two years post-transplant.18 19 Graft reinfecction is generally initiated by a lobular hepatitis, frequently asymptomatic and occurring commonly between the first and fourth months after transplantation. This hepatitis resolves very occasionally but most often evolves into a chronic hepatitis.20 Evolution into severe hepatitis with graft loss is also well documented21 22 and early histological recurrence may be associated with an increased risk of disease progression.23 Liver cell necrosis with conspicuous increases in alanine aminotransferase activity is not a constant finding, so prospective histological surveillance is required for the management of patients who were transplanted for HCV.24 Indeed, there is a poor correlation between serum aminotransferase values and the severity of graft damage.25

Early studies suggested that the survival of patients transplanted for HCV was not inferior to the survival of

Abbreviations used in this paper: HCV, hepatitis C virus; IFN, interferon; HBV, hepatitis B virus; CMV, cytomegalovirus.
patients transplanted for other liver conditions. For instance, Feray et al. reported that the five-year survival was not significantly different from that observed for a control group (80% vs. 89%).23 This observation was not supported by other investigators who described inferior graft (56% vs. 74%) and patient (66% vs. 81%) survival of patients with HCV when compared with a control group. The same investigators also found a higher graft rate for the HCV infected patients.24 Gane et al. found no significant difference in the five-year survival of patients transplanted for HCV compared with other indications (70% vs. 69%) (table 1). The incidence of cirrhosis was 8% after five years and eight of 149 patients had lost their grafts as a direct result of graft reinfection.25 The same study showed, as did other series,26 27 that the risk of significant bacterial infection may be increased when transplantation is undertaken for HCV infection. The study by Boké et al. could not demonstrate that recurrent HCV had a significant impact on mortality during the first post-transplant decade. In that analysis, a single patient developed cirrhosis during the first two post-transplant years, but none lost the graft as a direct result of recurrent viral infection.28

As for hepatitis B virus (HBV) infection, a rapidly progressive form of fibrosing cholestatic hepatitis has been associated with HCV recurrence in some patients. Described initially in a heart transplant recipient who acquired HCV from the donor,29 it has been reported in as many as 8% of patients with HCV recurrence. The prognosis is poor and most affected patients require early regrafting.30 No data have been published until recently on the efficacy of antiviral treatment in this form of HCV recurrence.31

Clearly, HCV recurrence can precipitate early graft loss and is associated with the development of cirrhosis in some patients. The impact of recurrent infection is underestimated by studies with short term follow up, and the true impact may not be observed until the second decade after transplantation. Although reinfection is associated with minimal graft damage for a number of patients, others have aggressive infection. It seems likely that those studies which failed to show an impact of recurrent infection on graft and patient survival may require larger numbers of patients, with longer follow up or better selected controls.

Pathogenesis of hepatitis after HCV recurrence

The variable consequences of liver disease associated with recurrent HCV infection suggest that different viral and/or host factors are important in determining the clinical outcome, but their impact remains unclear.

The serum viral titre seems to be higher after transplantation, probably as a consequence of immunosuppression. There is no clear correlation between viral titre and histological changes,32 suggesting that HCV may not be directly cytopathic. A potentially important factor may be the effect of genotype on disease recurrence. The influence of viral genotype on disease progression and the risk of developing hepatocarcinoma in the immunocompetent patient are uncertain. The liver transplantation model where the duration of infection is known might permit an improved understanding of the clinical relevance of genotypes to disease progression. Initial studies suggested that genotype 1b was associated with more aggressive recurrence.33 34 However, the predominance of genotype 1b in the transplanted population may have influenced that observation. In Gane et al.'s study the presence of genotype 1b seemed to be associated with an unfavourable clinical course with more severe hepatitis and cirrhosis.35 These findings were not supported by Wright et al. who examined a cohort of 124 patients that included equivalent numbers of genotypes 1b and 1a.36 Furthermore, genotype 1a was claimed to be predominant among patients regrafted for recurrent HCV infection37 and might be most frequently associated with the development of fibrosing cholestatic hepatitis.38 Little is known about the influence of viral quasispecies on the outcome of recurrent HCV infection after transplantation. It seems that the heterogeneity of viral quasispecies decreases after transplantation probably because of the decreased immunity mediated selective pressure that results from immunosuppressive therapy.39 40 These results can only be considered preliminary and more patients must be studied to address this issue. The potential impact of hepatitis G virus coinfection on the clinical course of HCV infected recipients has also been studied and there seems to be no association between hepatitis G virus co-infection and the severity of liver disease after transplantation.36 38

It is likely that other immune responses influence the severity of recurrent HCV infection. Rejection, and its management, may be important determinants of outcome. Thus, according to Sheiner et al. multiple rejection episodes are frequently associated with recurrent hepatitis. Corticosteroid resistant rejection requiring OKT3 treatment was associated with early and frequent recurrence.41 Such observations might encourage the preference for tacrolimus as primary immunosuppression for patients transplanted for HCV as it has been shown to diminish the requirement for corticosteroids in comparison with cyclosporin treated patients.42 However, Gane et al. found no difference between the frequency and severity of recurrent HCV infection in tacrolimus treated compared with cyclosporin treated patients.43 The impact of OKT3 induction on recurrent HCV infection is also disputed.41

The impact of rejection and immunosuppression on HCV recurrence needs to be carefully defined in future studies. It seems likely that these related factors act by influencing the immune response, rather than simply increasing viral titre. In addition, the nature of the immune response, with deviation towards a Th2 cytokine profile and diminution of the inflammatory reaction, might favour a more cytopathic effect for HCV, as has been observed for other infectious diseases.42

Gretch et al. found that the donorrecipient HLA match at the DQ loci is associated with histological recurrence.43 A similar observation has been for HBV recurrence,44 but this observation was not upheld by Gane et al. in their analysis of HCV recurrence.

The possible relation between cytomegalovirus (CMV) viraemia and HCV recurrence has also been studied.45 Patients transplanted for HCV who developed CMV viraemia had a significantly greater risk of severe recurrent

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration of follow up (y)</th>
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<th>Graft loss related to HCV recurrence (%)</th>
<th>Cirrhosis/cholestasis hepatitis (%)</th>
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<td>8/149</td>
<td>10/149</td>
</tr>
<tr>
<td>Boké et al</td>
<td>5</td>
<td>62</td>
<td>0/61</td>
<td>0/61</td>
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<tr>
<td></td>
<td>10</td>
<td>62</td>
<td>0/61</td>
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</table>

Note: patient survival is comparable in the HCV and control groups, but the rate of graft loss related to HCV infection (different in the two studies, 5.4% vs. 0%) was not compared with the controls.

Table 1 Long term natural history of HCV recurrence after liver transplantation

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hepatitis. As CMV viraemia is often associated with more rejection episodes and increased immunosuppression, it is difficult to determine the direct impact of CMV infection on HCV recurrence. CMV infection may be associated with high levels of tumour necrosis factor α, which may in turn be a mediator in the pathogenesis of HCV infection.46

**Treatment of HCV recurrence**

**TREATMENT OF ESTABLISHED INFECTION**

The use of IFN monotherapy for recurrent HCV infection has been described in three published studies (table 2). The first study described 11 patients treated for six months at a dose of 3 million units thrice weekly. A biochemical response was observed for a single patient, and no rejection was observed.49 Wright et al monitored patients’ response to four months’ treatment with IFNα-2b at a dose of 3 million units thrice weekly. A biochemical response was observed in 28%, but a completely negative PCR result was not achieved for any, and post-treatment titres were not significantly reduced from those before treatment. In that study, a biochemical response was predicted by low serum bilirubin, low viral titre, and a long interval between transplantation and the start of treatment. No histological improvement was observed after treatment. A single episode of steroid responsive graft rejection was observed.48

In contrast, Feray and colleagues47 reported significant IFN associated morbidity. Fourteen patients were treated for six months at a dose of 3 million units thrice weekly. Chronic rejection developed in 35% of the treated group compared with only 3% in a non-treated group. The biochemical response rate was 23%, and a reduction in viral titre was achieved in 57% of the treated patients. Histological improvement was observed in two patients.

These observations do not support the widespread use of IFN monotherapy for treatment of established graft infection.

Ribavirin has also been used as monotherapy for recurrent HCV.50 51 Two studies of a total of 16 patients have been reported, and the results appear concordant. Normalisation of aminotransferase values was observed in 50% of treated patients, which reversed on discontinuation of treatment. Viral titres may diminish, but virus can always be detected during treatment. Histological improvement may be observed in patients with a biochemical response.50 No episode of rejection were observed and side effects seemed comparable with those experienced by an immunocompetent population.

Combination IFN–ribavirin, followed by ribavirin alone, may provide an alternative approach (table 2).52 We have treated 21 patients using this protocol. After six months of combination therapy, the biochemical response rate was 100%, and 48% of treated patients were serum PCR negative. During subsequent ribavirin monotherapy, aminotransferase values remained normal for all but one of 18 patients who were tolerant of ribavirin. The improvement in histological activity, observed for all patients after six months of combination therapy, was maintained by all but one patient who remained on ribavirin for a further six months. Three patients with pre-existing renal insufficiency developed anaemia of sufficient severity that ribavirin had to be stopped. Rejection was not observed during this study. The immunosuppressive effect of ribavirin may influence the development of rejection during combination therapy.51 54

Patients with graft failure associated with recurrent HCV infection might be considered for regrafting. Few data are available, but those of Sheiner et al suggest that regrafting should be undertaken before the development of renal insufficiency and infectious complications.55 It is noteworthy that in this series the prevalence of genotype 1a in patients considered for regrafting was high, compared with the overall prevalence of patients transplanted for HCV cirrhosis. Among the nine patients who survived the post-operative period, a single patient developed fatal HCV recurrence. Thus, it seems that regrafting is a realistic option as long as it is considered in due time.

**PROPHYLACTIC TREATMENT**

The use of IFN before transplantation poses two problems: tolerance of IFN is frequently poor in patients with decompensated cirrhosis, and efficacy is mostly lacking at this advanced stage. However, in our experience (unpublished data), which is similar to that of Van Thiel et al,56 the clearance of HCV RNA before transplantation helps to prevent HCV recurrence after transplantation.

Another theoretical approach, currently impractical, is immunoprophylaxis with specific anti-HCV immunoglobulin, similar to the prevention of HBV infection. However, immunoprophylaxis was not shown to be protective in an animal model.57 Nevertheless, a lower rate of HCV recurrence has been reported for patients receiving anti-HBs hyperimmune globulin.57 These results, suggesting a potentially protective role for anti-HCV antibodies, are difficult to interpret in the context of a dual viral infection (HBV and HCV). In addition, the anti-HCV titre of such preparations is likely to be low as anti-HCV positive blood donors are excluded from donating blood.

**Conclusion**

Recurrent HCV infection and hepatitis remain an unresolved challenge in liver transplantation. Although HCV reinfection is universal, only 50% of patients seem to develop chronic hepatitis during short term follow up. The prevalence increases as the length of follow up increases. The impact of HCV recurrence on long term survival, the risk of developing cirrhosis and graft loss warrants further evaluation. The subgroup of patients who develop fibrosing cholestatic hepatitis deserves special attention. The natural history of HCV recurrence is better understood as a result of retrospective studies, but only prospective studies will help to clarify the virological and histological course of recurrent infection. An improved understanding of immune responses to HCV infection might explain why some patients develop recurrent hepatitis, yet others experience viraemia without significant graft pathology. With respect to antiviral treatment, IFN has little efficacy and may be associated with the development of acute and chronic rejection. Early intervention with combination IFN–ribavirin therapy may be a promising alternative, but this requires confirmation in prospective

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>No of patients</th>
<th>Biochemical responders (%)</th>
<th>PCR negative (%)</th>
<th>Histological improvement (%)</th>
<th>Rejection (%)</th>
</tr>
</thead>
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<tr>
<td>Wright et al57</td>
<td>IFN 5MU×3/W (6 months)</td>
<td>11</td>
<td>9</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Wright et al58</td>
<td>IFN 5MU×3/W (4 months)</td>
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<td>28</td>
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<td>4</td>
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<td>Feray et al59</td>
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<td>23</td>
<td>0</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Cattral et al59</td>
<td>Ribavirin (6 months)</td>
<td>9</td>
<td>22</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Gane et al61</td>
<td>Ribavirin (6 months)</td>
<td>7</td>
<td>57</td>
<td>0</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>Bizollon et al52</td>
<td>IFN 5MU×3/W +ribavirin (6 months)</td>
<td>21</td>
<td>100</td>
<td>48</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>
studies. The potential benefit of maintenance ribavirin treatment needs to be established. The alternative approach may aim to eradicate the infection before transplantation, but this option may also result in safer and better treatment than IFN. Finally, the development of xenotransplantation and the use of organs resistant to human pathogens like HCV may possibly be a reality for the distant future.

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