Antiviral treatment in patients with hepatitis C virus-related cirrhosis awaiting liver transplantation

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Abstract: End stage liver disease due to hepatitis C virus (HCV) infection is the most common indication for liver transplantation (LT) worldwide. Regretfully, infection of the graft by HCV occurs almost universally after LT, causing chronic hepatitis and early progression to cirrhosis in a significant proportion of recipients. Moreover, graft and patient survival are significantly worse in patients undergoing LT for HCV-related cirrhosis than in those transplanted for other indications. Therefore, many LT centers consider antiviral treatment with interferon and ribavirin the mainstay of managing recurrent HCV disease in LT recipients. The optimal time to start treatment is unclear. In most instances, treatment is initiated when histological evidence of disease recurrence, either at protocol or on-demand liver biopsies, is observed after LT. However, antiviral treatment initiated before LT is a potential option for some patients for two reasons: first, clearing or suppressing HCV before LT may reduce or eliminate the risk of recurrent hepatitis C in the transplanted liver and thereby improve survival; second, clearing HCV in cirrhotic patient may halt disease progression and avoid the need for transplantation. In this article, the results obtained by pre-transplant antiviral regimens administered to HCV-positive cirrhotic patients awaiting LT are discussed.

Keywords: hepatitis C, antiviral therapy, liver cirrhosis, liver transplantation

Chronic infection with hepatitis C virus (HCV) is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) in Western countries and accounts for about half of the indications for liver transplantation (LT) worldwide (Berenguer et al 2000). Although LT is effective for treating decompensated cirrhosis and small HCC secondary to hepatitis C, HCV re-infection of the graft is virtually the rule among patients in whom serum HCV RNA is detectable at the time of the transplant operation (Gish et al 2005). Moreover, the rate of hepatic fibrosis progression is much faster in LT recipients with recurrent hepatitis C than in immune-competent patients with chronic hepatitis C (Bizollon et al 1999; Berenguer et al 2000). As a result, graft cirrhosis is observed in approximately 30% of HCV-positive recipients five years after LT, resulting in 23% excess mortality and 30% excess graft loss (Forman et al 2002). Since the availability of donor organs is limited, and the resources invested for each liver transplant are increasing, strategies to improve the outcome of LT for hepatitis C need to be devised.

Donor and recipient factors, viral factors, and transplant-associated events have been linked with an increased severity of HCV disease. Considering the viral factors, it is well known that HCV particles circulating in the blood at the time of surgery, is the likely source of virus that reinfects the new graft, although other extra-hepatic sources of HCV may contribute (McCaughan et al 2004). Indeed some studies have linked a high viral load before LT with a more severe HCV recurrence after LT (Charlton et al 1998; Berenguer et al 2000). Thus, the strong rationale to treat HCV

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infection before LT, while the patient is on the waiting list, is that administering antiviral treatment pre-transplant may prevent graft re-infection, hence reducing the risk of early fibrosis progression in the graft and, hopefully, improving graft and patient survival. Moreover, HCV clearance may halt further disease progression among LT candidates, who might thus avoid or delay LT (Terrault et al 2006).

Antiviral therapy for HCV-related cirrhosis

Antiviral treatment of HCV-positive immune-competent cirrhotic patients is currently based on the combination of pegylated interferon α-2a (Pegasys, Roche, USA) or 2b (PEG-Intron, Schering Plough, USA) in association with ribavirin (Copegus, Roche, USA or Rebetol, Schering Plough, USA); in the near future, the therapeutic armamentarium for hepatitis C will be expanded to include new drugs, such as protease and polymerase inhibitors, that are expected to increase the effectiveness of interferon-based treatment regimens (Toniutto et al 2006).

With current treatment regimens, the rates of sustained virological response (SVR) among cirrhotics can be as high as 40%–50% (Manns et al 2001; Fried et al 2002; Hadziyannis et al 2004; Toniutto et al 2006). However, in the large registration clinical trials from which these data were generated, patients with signs of portal hypertension or decompensated liver disease were not included; therefore, these rates cannot be extrapolated to sicker patients such as those on a waiting list for LT.

Antiviral therapy for HCV-related cirrhosis in patients awaiting liver transplantation

To date, four studies have investigated the efficacy and safety of antiviral treatment in patients with HCV-related cirrhosis awaiting LT: in three, patients received interferon α-2b (Intron-A, Schering Plough, USA) plus ribavirin (Crippin et al 2002; Forns et al 2003; Everson et al 2005), and in one, monotherapy with standard interferon α-2b administered daily (Thomas et al 2003). The main clinical and virological features of these studies are summarized in Table 1. Furthermore, a recent study has evaluated the efficacy and safety of the combination of pegylated-interferon α-2b plus ribavirin in patients with decompensated HCV-related cirrhosis, of whom some were subsequently transplanted (Iacobellis et al 2007).

The study by Thomas and colleagues (2003) was based on the aforementioned assumption that the greater the HCV viral load at the time of LT, the earlier clinically evident post transplantation HCV recurrence occurs (Charlton et al 1998).

Table 1 Summary of the main clinical and virological features of studies evaluating the antiviral therapy in HCV-positive cirrhotic patients awaiting liver transplantation

Author (year)	N. of pts	Treatment regimen	Mean duration (months)	On treatment viral response (%)	SVR (%)	HCV recurrence (%)	Adverse events[§] (%)
(Crippin et al 2002)	15	Group A (3 pts): IFN 1 MU qd Group B (6 pts): IFN 3 MU qd Group C (6 pts): IFN 1 MU qd plus RIB 400 mg bid	2	33	NA	100	87
(Thomas et al 2003)	20	IFN 5 MU qd	14	60	NA	67	15
(Forns et al 2003)	30	IFN 3 MU qd plus RIB 800 mg qd	3	30	NA	33	30
(Everson et al 2005)	102	IFN 1.5 MU tiw plus RIB 600 mg qd IFN increased to 3 MU tiw at week 2 RIB increased by 200 mg weekly after week 4	NR	46	24	20	65

Abbreviations: IFN, interferon; RIB, ribavirin; NR, not reported; SVR, sustained viral response; NA, not applicable.
Notes: [§]Events that caused dosage reduction or discontinuation of antiviral therapy.

Twenty HCV-positive cirrhotic patients (67% infected by genotype 1) were treated with an aggressive schedule using interferon α-2b 5 MU daily dose for a mean of 14 months before LT. The proportion of patients who cleared the virus during treatment was 60% and, more importantly, 4 of the 12 patients (33%) who achieved this result did not have evidence of HCV recurrence after LT during a mean follow up of 34 months. This antiviral regimen was generally well tolerated, although all patients required granulocyte-stimulating factors (GCSF) in order to maintain their white blood cell count above 1500 cells/mm^3. In the study conducted by Crippin and colleagues (2002), 15 HCV-positive cirrhotic patients in Child-Pugh class B or C, approaching the top of their waiting lists, were randomized to receive, until LT, a regimen based either 1 MU or 3 MU three times weekly of standard interferon α-2b, or the association of 3 MU of standard interferon α-2b three times weekly plus 400 mg twice daily of ribavirin. It is important to note that in this study less than half of the screened patients met the inclusion criteria, thrombocytopenia and leukopenia being the most common reasons for exclusion. Absence of circulating HCV RNA by a sensitive polymerase chain reaction assay at the time of LT was achieved by 5/15 (33%) patients; three of these patients had HCV RNA levels undetectable by bDNA signal amplification at baseline. Two further patients underwent LT during antiviral therapy, one with circulating HCV RNA undetectable by bDNA signal amplification but detectable by PCR, and one who achieved only a small (less than one $\log_{10}$) decline in HCV RNA levels; in both patients, HCV infection recurred after LT. The study was interrupted early because a relevant proportion of patients experienced serious adverse events during treatment, leading the authors to conclude that patients with advanced liver disease should not be candidate for antiviral therapy. More encouraging results have been reported in the study conducted by Forns and colleagues (2003), in which 30 HCV-positive cirrhotic patients (25 infected by genotype 1) were treated, until the transplant operation, with the combination of 3 MU daily of interferon α-2b plus 800 mg daily of ribavirin, started when the expected time for LT was less than four months. At the time of their inclusion in the study, half of the patients were in Child-Pugh class B or C. Among the 9 (30%) patients who achieved SVR and underwent LT, 6 (67%) remained free of HCV recurrence after a mean follow-up of 46 weeks. In analogy to what occurs outside the LT setting, the factors independently associated with SVR were the viral load at baseline and its decrease >2 $\log_{10}$ at week 4 of therapy. Side effects related to antiviral treatment were frequent and caused a dose reduction in 19 (63%) of the 30 treated patients. In the more recent study by Everson and colleagues (2005), 102 patients with HCV-related cirrhosis received escalating doses of standard interferon and ribavirin. The initial treatment schedule required interferon α-2b 1.5 MU three times weekly, plus ribavirin 600 mg daily. The interferon dose was increased to 3 MU three times weekly at week two, whereas the ribavirin dose started to be escalated only after week 4. Sixty-eight (67%) of the patients were in Child-Pugh class B or C, and the vast majority (70%) were infected by HCV genotype 1. The overall end of treatment and SVR rates were 46% and 24% respectively. Significantly higher virological response rates were observed in HCV genotype 2 and 3 infected patients in comparison to those infected by genotype 1 (60% Vs 11%). Eighty percent of the patients who achieved SVR and underwent LT were free of HCV recurrence in the graft after a mean follow-up of more than 6 months; however, only a small proportion of those listed and treated (15 out of 90 patients) were transplanted. Despite the use of erythropoietin and GCSF, adverse events requiring discontinuation of therapy occurred in 20% of patients. Finally, in a very recent study by Iacobellis and colleagues (2007), aimed to investigate the efficacy and safety of combination therapy with pegylated interferon α-2b plus ribavirin in treating HCV-related decompensated cirrhosis, 129 patients were enrolled. The inclusion criteria were HCV-related cirrhosis and hospital admission for ascites, variceal bleeding or hepatic encephalopathy. One month after the resolution, of the decompensated event with appropriate management, all patients were offered antiviral therapy, after explanation of expected benefits and potential risks. About half (66 patients) agreed to be treated whereas the remaining 63 patients, who did not, served as controls. The most common diagnosis at admission was ascites; 71% and 23% were classified in Child-Pugh class B and C respectively. The mean MELD score value was 14, but only 24% had a MELD score >18. About two thirds were infected by HCV genotype 1 and 22% of the treated patients were older than 65 years. Baseline characteristics of treated and untreated patients did not differ significantly, with the exception of hemoglobin levels, which were higher in treated patients than in controls. The treatment regimen employed was the combination of weekly 1.0 μg/Kg body weight of pegylated-interferon α-2b with oral ribavirin at a daily dosage of 800 or 1000 mg for body weights $<$ or ≥ 75 Kg, respectively, for 24 weeks. By intention-to-treat analysis, SVR was achieved in 43.5% of patients infected by HCV genotypes 2 and 3, and in 7% of those infected by genotypes 1 and 4. Only 41% of

treated patients completed the intended schedule of treatment. In fact, despite the liberal use of GCSF and erythropoietin, in 38% of the patients dosages of both pegylated interferon and ribavirin had to be reduced for hematological toxicity. Twenty-one percent of patients discontinued treatment for severe adverse events, mainly severe urinary or respiratory tract infections, occurring more frequently in Child-Pugh class C patients and in cases with neutrophil counts at baseline $\leq 2100/mm^3$. Although the mortality rates on treatment did not differ between patients and controls, a trend towards a higher probability of death, related to severe infection episodes, was observed in the treated group. At the end of a median follow up of 30 months, patients who achieved a SVR demonstrated a significantly better outcome than nonresponders and controls. As compared with the baseline value, the Child-Pugh score significantly improved at the end of follow-up in SVR patients and worsened both in nonresponders and in controls. There were nine deaths in the group of nonresponders and 15 among controls, mainly related to liver failure; moreover, one and four patients underwent liver transplantation due to progressive liver failure and/or development of HCC, respectively. All 13 patients who achieved SVR survived without LT.

Summary and conclusions

The strongest rationale to treat HCV-positive cirrhotics on the waiting list for LT is provided by the evidence that those who achieve SVR can benefit both in term of liver function, which improves, and HCV recurrence rate in the graft, which decreases. Furthermore, at least for a few patients, just being HCV RNA negative while on treatment at the time the transplant operation is performed may be sufficient to prevent post transplant HCV recurrence (Kuo et al 2006). It is important to note, however, that these results have been obtained in small and uncontrolled clinical studies, which enrolled overall less than 300 patients with a relative short period of follow-up. For these reasons, to date, to treat with antiviral therapy all HCV-positive patients who are listed for LT can not be recommended. Rather, these observations should stimulate a very important debate in the liver transplantation community, ie, if the actual organ allocation policy should be changed, conferring priority in the waiting list to HCV-positive patients treated with antiviral therapy who achieve virologic endpoints, either on or off treatment. Performing the LT when serum HCV RNA is undetectable could represent a promising way to prevent HCV recurrence, that is the most important predictor of reduced survival post LT. The rate of SVR is influenced, as in immunecompetent patients treated for chronic hepatitis C, by viral load at baseline, slope of HCV RNA decline during treatment and, most importantly, HCV genotype. In particular, the risk-benefit of antiviral treatment in cirrhotic patients infected by HCV genotype 1 is unclear, since SVR rates are extremely low. Since the tolerability of antiviral therapy in these very difficult to treat patients is limited, and, independently of neuthrophil counts, life threatening infections are not uncommon, it is often necessary to reduce the doses of both interferon and ribavirin. Moreover, only a limited proportion of patients with advanced and decompensated liver disease awaiting liver transplantation are eligible for therapy; they should not be treated outside clinical trials, to be conducted, under strict surveillance, preferably in experienced centers. The best way to manage antiviral therapy in HCV-positive patients awaiting LT is probably to start treatment as soon as patients are registered in the LT waiting list; this may allow the patients to be given a possible life-line, if their disease is to get worse sooner then expected. Furthermore, antiviral treatment should probably be stopped in the absence of early antiviral response. The subgroup of patients who could gain most from antiviral therapy before transplantation is that of patients with HCV-related Child-Pugh class A cirrhosis with HCC, preferentially related to HCV genotype 2 or 3 infection, scheduled to obtain an early liver transplant from a deceased donor or awaiting living donor LT.

Several questions remain unanswered and represent the goals of future studies. First of all, since SVR rates in HCV-positive patients awaiting LT treated with the combination of standard interferon plus ribavirin remain suboptimal, large clinical trials evaluating the efficacy of the combination of pegylated interferons with ribavirin are urgently needed. Secondly, it should be investigated whether the systematic use of GCSF and erythropoietin in preventing cytopenias during antiviral treatment allows higher SVR rates. A third, very important issue regards the possible benefit related to longer duration of antiviral treatment employing reduced doses of standard or pegylated interferon with or without ribavirin in terms of slowing fibrosis progression, in the absence of HCV clearance. Recent data coming from the HALT-C clinical trial (Everson et al 2006) clearly showed that patients with advanced liver diseases (ie, cirrhosis and platelets count $\leq 125000/mm^3$) previously non responders to antiviral therapy, when retreated with pegylated interferon α-2a in combination with ribavirin, achieved a SVR only in 9% of cases. Importantly, a benefit in reducing the progression of liver disease could be demonstrated only for patients who achieved a SVR. The HALT-C trial, therefore, does not

support the strategy to retreat for longer periods of time HCV cirrhotic patients, non responders to previous treatments, as far as the aim of treatment is to stop the progression of liver disease. Finally, the poor tolerability and limited efficacy of current treatment strategies highlight the need for alternative drugs able to induce a more vigorous HCV viral decline without prohibitive side effects. Several promising new compounds administered orally have been discovered and are currently undergoing clinical development. In particular, two HCV NS3 serine protease inhibitors, named bocepravir (Schering-Plough, USA) and telaprevir (Vertex Pharmaceutical, USA), alone or in combination with pegylated interferon, determine a 2 to 4 $\log_{10}$ reduction in HCV viral load along a short period of time, although with rapid insurgence of escape mutants. In LT centres where the time of the transplant operation can be predicted with reasonable accuracy, potent antiviral regimens including these new drugs might prove to be most effective when used, for a limited period of time, by HCV patients on the waiting list.

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