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Editorial

Antiviral therapy in HCV-infected cirrhotics awaiting liver transplantation: A costly strategy for mixed virological results ☆

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Hepatitis C virus (HCV)-related liver disease is the principal cause of cirrhosis and hepatocellular carcinoma and the leading indication for liver transplantation (LT) in Western countries. However, recurrent HCV infection is common in pre-transplant HCV RNA positive patients with an accelerated course, leading to cirrhosis in around 30% of patients five years after LT [1]. Given the impact of HCV recurrence on graft and patient survival, several treatment strategies have been evaluated in order to prevent or treat HCV infection: pre-transplantation antiviral therapy, pre-emptive therapy initiated soon after transplantation and therapy for established post-transplant chronic hepatitis. Although their likelihood of responding to peginterferon (Peg-IFN) plus ribavirin (RBV) is less than that identified in registration trials involving non-cirrhotic patients, those with compensated cirrhosis can achieve response rates of up to 50%, depending on their HCV genotype (41% for genotype 1, 73% for genotype 2–3) [2]. In patients with decompensated cirrhosis, the treatment of HCV infection has two main goals: first, the suppression of HCV viremia in LT candidates may reduce or eliminate the risk of recurrent infection [3–6], although the effect of reducing the pre-transplant viral load in order to decrease the severity of post-transplant disease progression is unknown but probably slight [7]; and second, in the longer term, HCV clearance in cirrhotic patients may halt disease progression and modify the natural history of the disease [8–10]. However, this approach has displayed certain limitations in HCV cirrhotic patients awaiting liver transplantation: a high prevalence of genotype 1, problems in achieving full doses of IFN and RBV because of side effects, and a risk of complications related to impaired liver function. As mentioned above, the objective is not to reduce the viral load at transplantation because this has not been shown to decrease the rate and severity of recurrence, in contrast to HBV cirrhotic patients. The aim is either to achieve a sustained virological response (SVR) at transplantation or an on-treatment serum HCV RNA clearance at transplantation. In the former case, a period of at least 24 weeks is required after the end of treatment, which may be too long and deleterious for patients awaiting LT. Few published studies have investigated the role of standard IFN with or without RBV in patients with decompensated HCV cirrhosis: all were performed in a single center only, were not controlled and varied considerably in terms of their objectives (prevention of recurrence, effect on the natural history of disease), and modalities (doses, duration, delay before LT) [3–6,8].

The study by Carrion et al. published in this issue of the Journal, is the first to have used Peg-IFN (alfa-2a 180 μg/week) plus RBV (dose adjusted to creatinine clearance, 400–1200 mg/d) therapy in 51 HCV-infected

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cirrhotic patients awaiting LT (median duration of therapy: 15 weeks; range: 1–57 weeks) matched with 51 untreated controls [11]. However, it is a case-control study, which is a major limitation because despite the accurate matching of control and treated patients, a randomized trial would have minimized any potential biases. Patients who previously did not respond to combination therapy, with a Child–Pugh score >12, recurrent encephalopathy, thrombocytopenia $<30 \times 10^9$/L or renal failure, were excluded. 80% of the treated patients were infected with genotype 1, 59% suffered from hepatocellular carcinoma, the median initial MELD score was 12 (6–25), and 45%, 43% and 12% were Child–Pugh classes A, B and C, respectively. The use of growth factors was permitted. This study aimed to evaluate both the prevention of HCV recurrence post-transplant and the risk of bacterial infections during therapy. Although the duration of follow-up is unknown, this study was not designed to assess the effect of antiviral therapy on modifying the natural history of cirrhosis. The virological response rate was high, since 24 treated patients (47%) achieved HCV RNA negativity during treatment, but only 15 (29%) were HCV RNA negative at the time of transplantation (drop outs $n = 3$, deaths $n = 4$, viral relapse $n = 2$) and 10 (20%) achieved an SVR after transplantation. The rate of SVR using Peg-IFN and RBV was similar to that reported previously with a daily, standard IFN regimen by the same investigators [5]. One explanation could be the large number of HCV RNA negative patients who were not transplanted due to death ($n = 4$) or drop-out ($n = 3$). High rates of dose reductions (49%) or discontinuation of treatment (43%) because of side effects impaired the efficacy of antiviral therapy. Although the results of short-term pre-transplant treatment using a standard IFN regimen (SVR after LT: 20%) [5] were very similar to those achieved with standard duration therapy (SVR after LT: 26%) [6], a longer duration of therapy requires further investigation in order to reduce the relapse rate. Of the patients achieving an SVR before LT, none experienced an HCV recurrence on the graft [6]. Post-transplant HCV recurrences in patients who achieved an on-treatment response without an SVR could be explained by the short duration of therapy and the persistence of HCV in a second compartment [5]. Liver HCV RNA levels in the explanted liver were not determined during this study, although this might be helpful when evaluating the risk of post-transplant recurrence. As reported by other studies using standard IFN, an early (or rapid) virological response and non-1 genotype were the strongest predictors of viral clearance during therapy [5,6,8,9]. The absence of a $\geqslant 2$ $\log_{10}$ reduction in HCV RNA between baseline and week 4 had a strong negative predictive value. This finding is highly relevant, as it will enable cessation of treatment in patients with a low probability of a response and thus reduces the risk of complications. The rate of SVR according to genotype is not reported in this study (viral clearance at the time of LT: 22% for genotype 1 patients), although in other studies the SVR rate with genotype 1 was around 7–13%, as compared to 43–67% with genotype 2–3 [5,8,9]. It should be noted that during all these studies, the antiviral therapy regimen was adapted to liver function (lower dosage of IFN or RBV, shorter duration of therapy) [5,8,9]. The other predictors of an SVR are the pre-treatment viral load [5,9], Child–Pugh score class A (genotype 1 only) and completion of treatment [6]. During the study in question, individuals who achieved an SVR had a significantly lower baseline viral load compared to virological responders who relapsed after transplantation (5.0 $\log_{10}$ IU/ml, 3.4–6.2 vs. 6.3 $\log_{10}$ IU/ml, 5.6–6.8; $p = 0.036$). Liver function was not predictive of a virological response in this cohort, although none of the patients with a baseline Child–Pugh score of C (or MELD > 18) achieved SVR.

The safety of Peg-IFN therapy is a major concern in patients with decompensated cirrhosis. The reported rates of neutropenia, thrombocytopenia, anemia, and episodes of infection or liver decompensation during therapy are 50–60%, 30–50%, 30–60%, 4–13% and 11–20%, respectively [5,6,8,9]. In the present study, the incidence of clinical decompensation (22% vs. 18%, $p = 0.62$) and survival (death before LT 8% vs. 2% $p = 0.06$; death 24 weeks after LT 8% vs. 12%; $p = 0.67$) were similar in treated patients and controls. However, the incidence of bacterial infection episodes (mostly spontaneous bacterial peritonitis and spontaneous bacteremia due to Gram-negative bacilli) was higher in treated patients (25%) than in controls (6%) ($p = 0.01$). A septic shock episode occurred in 10% of treated patients versus none in controls ($p = 0.05$). Variables independently associated with the occurrence of bacterial infections were antiviral treatment and a Child–Pugh score of B–C. In a cohort of 66 decompensated HCV-infected cirrhotics treated with Peg-IFN alfa-2b and RBV for 24 weeks vs. 63 controls, Iacobellis et al. showed that the odds ratios in treated patients were 2.95 for severe infection and 1.97 for death from infection. They reported that variables independently associated with infective episodes were Child–Pugh class C and a neutrophil count <900 μL during treatment [8]. In the study by Crippin et al. antiviral treatment in patients with a mean Child–Pugh score of 12 (±1.2) was the cause of life-threatening infections, which ultimately led to early discontinuation of the study [3]. Importantly, in the study by Carrion et al. the incidence of spontaneous bacterial peritonitis in patients who were not receiving norfloxacin was significantly higher in the treated group than in controls (log-rank = 0.012), whereas no difference was observed in patients who were receiving norfloxacin prophylaxis (log-rank = 0.62).

In summary, this study suggests that antiviral therapy using Peg-IFN regimens in HCV cirrhotic patients awaiting LT is possible with a relatively high rate of virological response (47%) and can prevent a recurrence of HCV, especially in patients with a non-1 genotype and an early (or rapid) virological response. The primary goals of treatment are either an SVR or an undetectable HCV RNA level at the time of LT, both of which significantly reduce the risk of post-transplant HCV recurrence. Because of the potential for serious adverse events, patients should be closely monitored during antiviral treatment and followed by centers with considerable experience of managing decompensated cirrhosis. This rate of severe infection during IFN therapy is similar to that observed in HBV cirrhotic patients who received pre-transplant IFN before the advent of nucleo(s)tide analogues [12]. The best candidates for therapy remain Child–Pugh class A patients whose virological response rate is high and in whom the risk of side effects is almost identical to that of controls. Antiviral therapy is currently not indicated in Child–Pugh class C patients (or MELD > 18) because of the high risk of septic complications during treatment and a low SVR rate. In Child–Pugh class B patients, treatment should be discussed on a case-by-case basis as a function of baseline factors for a potential response (i.e., genotype non-1, viral load) with virological monitoring at weeks 4 and 12. In this way, antiviral therapy can be discontinued after 4 or 12 weeks if there is no virological response. Antibiotic prophylaxis and the use of growth factors may facilitate antiviral therapy in patients with poor liver function. The risk/benefit ratio of treating Child–Pugh class B patients in order to prevent HCV recurrence still needs to be determined by randomized controlled trials. The new classes of potent and direct antiviral agents are not yet available for patients with decompensated HCV cirrhosis. However, it is probably this group of patients who will benefit the most, and the time has come for a shift towards novel therapeutic strategies.

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