Antiviral therapy in hepatitis C virus cirrhotic patients in compensated and decompensated condition

Angelo Iacobellis, Antonio Ippolito, Angelo Andriulli

Angelo Iacobellis, Antonio Ippolito, Angelo Andriulli, Division of Gastroenterology, “Casa Sollievo della Sofferenza” Hospital, IRCCS, San Giovanni Rotondo 71013, Italy

Author contributions: Iacobellis A and Andriulli A contributed equally to this work and wrote the paper; Iacobellis A and Ippolito A analyzed the data.

Correspondence to: Angelo Andriulli, MD, “Casa Sollievo della Sofferenza” Hospital, IRCCS, viale Cappuccini 1, San Giovanni Rotondo 71013, Italy. a.andriulli@operapadrepio.it

Telephone: +39-882-411263 Fax: +39-882-411879

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Abstract

The main goals of treating cirrhotic patients with antiviral therapy are to attain sustained viral clearance (SVR), halt disease progression, and prevent re-infection of the liver graft. However, while the medical need is great, the use of interferon and ribavirin might expose these patients to severe treated-related side effects as a large proportion of them have pre-existing hematological cytopenias. We have reviewed potential benefits and risks associated with antiviral drugs in patients with liver cirrhosis, due to hepatitis C virus (HCV) infection. In cases presenting with bridging fibrosis or cirrhosis, current regimens of antiviral therapy have attained a 44%-48% rate of SVR. In cirrhotic patients with portal hypertension, the SVR rate was 22% overall, 12.5% in patients with genotype 1, and 66.7% in those with genotypes 2 and 3 following therapy with low doses of either Peg-IFN alpha-2b and of ribavirin. In patients with decompensated cirrhosis, full dosages of Peg-IFN alpha-2b and of ribavirin produced a SVR rate of 35% overall, 16% in patients with genotype 1 and 4, and 59% in those with genotype 2 and 3. Use of hematological cytokines will either ensure full course of treatment to be accomplished with and prevent development of treatment-associated side effects. Major benefits after HCV eradication were partial recovery of liver metabolic activity, prevention of hepatitis C recurrence after transplantation, and removal of some patients from the waiting list for liver transplant. Several observations highlighted that therapy is inadvisable for individuals with poor hepatic reserve (Child-Pugh-Turcotte score ≥ 10). Although SVR rates are low in decompensated cirrhotics due to hepatitis C, these patients have the most to gain as successful antiviral therapy is potentially lifesaving.

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Peer reviewer: Ramsey Chi-man Cheung, MD, Professor, Division of GI & Hepatology, VAPAHC (154C), 3801 Miranda Ave, Stanford University School of Medicine, Palo Alto, CA 94304, United States

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INTRODUCTION

Extensive fibrotic deposition in advanced hepatitis C virus (HCV) liver disease is the histopathological hallmark of a chronic necro-inflammatory process that involves parenchymal cells. Progressive derangement of normal liver architecture correlates with a reduction in liver synthetic function and brings to its late clinical expressions of decompensation, such as intractable ascites, hepatic synthetic failure, encephalopathy, jaundice, variceal bleeding, and hepatocellular carcinoma. Once cirrhosis is present, the process is generally considered as irreversible and predisposing to high mortality risk with a survival rate of 50% at 5 years[1]. A mathematical model of the natural history of chronic hepatitis C projected number of cases with cirrhosis to increase by more than 50% by 2010[2]. As a result, there will be a dramatic increase in the number of cases with complications of liver failure throughout the next three decades.

Once decompensation complicates liver cirrhosis, liver transplantation is the only successful therapeutic option. However, the limited number of organ donors as well as impairment in age-related cardiovascular, renal, and pulmonary functions, renders this option unlikely for the majority of patients. In addition, age over 65 years is commonly considered as an exclusion criterion.
to enlist patients for liver transplant. Exploring new therapeutic options to offer patients with HCV end-stage liver cirrhosis is a critical need, as cirrhotics who are never listed for liver transplant could still potentially benefit from non-surgical therapy.

In advanced liver cirrhosis, antiviral therapy is currently not recommended despite the fact that theoretical benefits of treating HCV-related patients with or without compensated cirrhosis would be an improvement in liver histology, reversal of established cirrhosis, and prevention of life-threatening complications. Despite this, a large proportion of these patients have pre-existing neutropenia, thrombocytopenia, and anemia that will tend to worsen with the use of interferon and ribavirin, exposing them to potentially severe side effects. We will review this topic with the intent to highlight potential benefits and risks associated with antiviral therapy in patients with compensated and decompensated cirrhosis due to HCV infection.

**HCV CIRRHOSIS IN COMPENSATED PHASE**

Compensated cirrhosis is defined by the absence of clinical complications and presence of both preserved hepatic synthetic function and adequate bone marrow reserve. Post-hoc analyses of patients with bridging fibrosis or compensated cirrhosis included in two international, registrative trials on the efficacy of Peg-IFN and ribavirin, produced a 43% rate of sustained viral clearance (SVR) by 48 wk administration of once weekly Peg-IFN alpha 2a 180 μg plus ribavirin 1000-1200 mg/d[3]. A similar rate of 44% was seen in those treated with Peg-IFN alpha-2b 1.5 μg/kg weekly plus ribavirin 800 mg/d for 48 wk[4]. From previous trials, data on cirrhotic patients could not be retrieved separately from those with bridging fibrosis, so that exact figures of SVR rate in cirrhotics remain to be determined. Moreover, cirrhotics enrolled in these studies were commonly in a Child-Pugh-Turcotte (CPT) class A, had as a rule a compensated disease, and slightly abnormal hematological parameters; moreover, no information was usually given on the degree of portal hypertension.

The first study proving the benefits of antiviral therapy in cirrhotics with signs of portal hypertension, a subset of patients with more advanced cirrhosis than the cohort of cirrhotics enrolled in registrative trials, was the one published by Di Marco et al[5]. In the study, a branch of 51 cirrhotics received 1 μg/kg per week of Pegylated-interferon alpha-2b plus oral ribavirin at a fixed dose of 800 mg/d for 52 wk. By intention-to-treat analysis, a sustained virologic response (SVR) was achieved by 11 patients (21.6%), with a therapeutic efficacy poorest in those infected with genotype 1 and 4 (6 of 45, 13.3%) than in those with genotypes 2 and 3 (5 of 6, 83.3%). All responders achieved negative HCV-RNA during the first 12 wk of treatment, and no subject still positive at this time evaluation became negative later despite continued treatment. The median WBC count decreased from baseline, particularly during the first two months of treatment. Five patients stopped Peg-IFN due to neutrophil counts < 0.75 × 10³/dL, but none of them developed infections. Cumulative incidence of events was significantly higher in patients without an SVR: disease deterioration occurred only in 6% of patients with SVR as compared to 38% of non-responders. This study established the effectiveness of antiviral therapy in the subgroup of patients with severe portal hypertension, although it must be emphasized that entry criteria for the trial excluded patients with clinical, biochemical, or hematological decompensation of the liver disease.

Safety of combination therapy in cirrhotics is a major concern. Bone marrow suppression by administration of both standard or Peg-IFN-alpha leads to significant decrease in all 3 lineages of the hematopoietic system, whereas anemia through haemolysis is more a sequela of ribavirin therapy[6]. Absolute neutrophil and lymphocyte counts typically decrease by 30% to 50% of baseline values during therapy[7]. In a recent analysis of patients treated at a single referral center, where basal neutropenia was not an exclusion criterion, therapy was safely accomplished despite decreases in neutrophils below the usual levels that lead to dose reduction or drug interruption[8]. No patients who developed infections had a pre-existing neutropenia (below 1500 cells/mL), and none developed neutropenia of less than 750 cells/mL at any point during treatment. Although the use of interferon in cirrhotics with neutropenia is usually not recommended, there is no evidence, up to now, of a significantly higher risk of severe infections or death correlated with interferon therapy in cirrhotics, a concern supported by the studies of Heathcote and Di Marco, where none of the cirrhotics with interferon-induced neutropenia of less than 750 cells/mL developed serious infection or sepsis[9,10].

It is currently recommended that development of leukopenia during antiviral therapy, an event that develops in 15%-20% of cases[9], to be managed by modification or withdrawal of drugs. This recommendation may potentially affect achieving an SVR, being the therapeutic outcome dependent on both dose and duration of currently administered drugs[10]. Hematopoietic cytokines, such as granulocyte colony-stimulating factor (G-CSF), at the weekly dosage of 300 μg, can reverse neutropenia, enabling patients to remain on full dosage and duration of therapy[11,12]. However, G-CSF is prescribed less frequently than erythropoietin, likely for two reasons: First, ribavirin-induced anaemia is more common than IFN-induced neutropenia and, secondly, practitioners are probably less responsive to neutropenia than to anaemia being the latter more often symptomatic than neutropenia. As regards to chronic hepatitis C, no official guidelines have been set for the use of G-CSF, probably because of the absence of firm data of the benefit of the cytokine administration in increasing SVR while reducing infections.

Treatment of HCV-infected patients induces hemoglobin drop in the majority of patients[13]. The anemia is of “mixed” type: Ribavirin induces a dose-dependent hemolytic anaemia, whereas IFN alpha suppresses eryth-
Table 1  Summary features of trials of antiviral therapy in HCV-infected cirrhotics with signs of hepatic decompensation

| Author            | Yr | No. of patients | Type of IFN | Dosage | RBV | Dosage per day | Length of therapy | Genotype 1 (%) | CPT score | MELD score | Decompensated (%) | Overall SVR n (%) | Genotypes 1 and 4 | Genotypes 2 and 3 | SVR n (%) |
|-------------------|----|-----------------|-------------|--------|-----|---------------|------------------|----------------|-----------|------------|-------------------|-------------------|----------------|----------------|-----------|
| Crippin et al[34] | 2002 | 15              | IFN α2b     | (1) 1 MU | (2) 3 MU | Yes/ No | 800 mg | Mean time: 1.95 mo (range 0.25 to 5 mo) | 93 | 11.9 ± 1.2 | No data | 100 | 0 | 0 |
| Thomas et al[35]  | 2003 | 20              | IFN α2b     | 5 MU/d  | No   | Yes/ No | Until the day of transplantation (14 ± 2.5 mo) | 63 | 10 ± 0.5 | 13.0 ± 2.5 | 100 | 4 (20) | 2 (10) |
| Forns et al[36]   | 2003 | 30              | IFN α2b     | 3 MU/d  | Yes  | Yes/ No | 800 mg | 12 wk | 6 mo for genotype 2 and 3 | 85 | 7.4 ± 2.3 | No data | 43 | 6 (20) | 3 (12) |
| Everson et al[37] | 2003 | 124             | IFN α2b     | Increasing doses until standard dose | Yes  | Yes/ No | 800 or 1000 mg | 6 mo | 8 ± 1.2 | 14.2 ± 2.7 | 100 | 13 (19.7) | 3 (7) |
| Iacobellis et al[38] | 2007 | 66              | PEG-IFN α2b | 1 μg/kg | Yes  | Yes/ No | 800 or 1000 mg | 6 mo | 8 ± 1.2 | 14.2 ± 2.7 | 100 | 13 (19.7) | 3 (7) |

*Child A 15 (50%), B 13 (43%), C 2 (7%).

Several lines of evidence have supported the hypothesis that the fibrinolytic component of cirrhosis is a reversible process[21-26]. SVR is the “sine qua non” to pursue his treatment. The most striking result of recent reports on antiviral therapy in HCV-infected cirrhotic patients who sustained one or more episodes of liver decompensation are available in the literature[33-36] (Table 1): The results indicate that these patients might tolerate current antiviral regimens. How antiviral therapy is commonly deferred in cirrhotics with signs of liver decompensation, due to even more compelling concerns over treatment-induced side effects. Along with the progression of liver disease, a reduction in the capacity to remove endotoxin and bacteria from the bloodstream, due an acquired immunodeficiency state, is observed in these patients[39]. However, the majority of cirrhotics with HCV infection have reasonably stable hepatic function after a successful treatment of a compensated event and, therefore, might be suitable candidates for antiviral therapy. It seems conceivable that tolerance of antiviral therapy in this particular setting of patients might be extremely poor due to their advanced age, as adherence to combination therapy is negatively influenced by increasing patient’s age[40]. In addition, impaired age-related cardiovascular and pulmonary functions may reduce tolerance of ribavirin-induced anemia, while impaired renal function by increasing blood levels of ribavirin (primarily cleared by kidney) may worsen anemia. Finally, insulin resistance secondary to HCV infection may further impair response to combination therapy[41]. Several reports on antiviral therapy in HCV-infected cirrhotic patients who sustained one or more episodes of liver decompensation are available in the literature[32-36] (Table 1): The results indicate that these patients might tolerate current antiviral regimens. However, unstandardized dosages of antiviral drugs that have been administered for a variable and different treatment length may have underestimated and differentiated outcomes and virologic response rates in previous reports. After reviewing existing experience, the International Liver Transplantation Society Expert...
Panel issued guidelines, in 2003, for the use of interferon-based therapy in patients with cirrhosis, strongly considering therapy in those with a CTP score ≤ 7, and possibly in those with a score of 8 to 11 (Table 2). In the low-accelerating dosage regimen, starting doses were 1.5 MU thrice weekly for conventional interferon, 0.5 μg/kg per week for Peg-IFN alpha 2b, or 90 μg/wk for Peg-IFN alpha 2a, given alone or in combination with a ribavirin dose of 400 mg/dL.[32] Dose adjustments for each of the two drugs were made every 2 wk as tolerated to achieve optimal effective doses. Using an initially low, accelerating regimen of non-pegylated interferon plus ribavirin, 39% of 102 patients experienced clearance of HCV-RNA on treatment, and 21% attained an SVR, 11% with genotype 1, and 50% with genotypes 2 and 3.[33] Moreover, of patients with SVR, none relapsed after liver transplantation.[33] By including Peg-IFNs, further improvement in efficacy can be expected. In our initial investigation, Peg-IFN alpha 2b (1.0 μg/kg) plus standard dose of ribavirin were administered for a short treatment duration (24 wk for all genotypes) to decompensated cirrhotic patients.[33] The overall SVR rate attained with this suboptimal regimen of therapy amounted to 19.7% (13 of 66 treated cases), higher efficacy (43.5% of SVR) being found in genotype 2 and 3 infection than in genotype 1 infection (7%). Therapy was tolerated by patients, at a remarkable exception of individuals with very advanced liver disease (CTP score > 10) who experienced severe life-threatening side effects.

Based on our initial investigation, we went further to determine whether currently recommended dosages of Peg-IFN and ribavirin for the standard length of treatment could be safely tolerated in decompensated cirrhotic patients. An ongoing protocol has been set up at our institution where all cirrhotic patients with a CTP score ≤ 9 and a decompensated event that abated with common management are offered therapy with Peg-IFN alpha-2b (1.5 μg/kg) and ribavirin (800-1000 mg for genotypes 2 and 3, and 1000-1200 mg for genotypes 1 and 4) for the recommended treatment duration (48 and 24 wk for genotype 1 and non-1, respectively) (submitted, unpublished data). In this program, at the end of the 24 wk follow-up period off therapy, 35% of our end-staged cirrhotics cleared the HCV infection, 16% of patients with genotype 1 and 4, and 59% of patients with genotype 2 and 3. Almost 60% of patients tolerated full dosage and duration of treatment, whilst 18 (19.1%) patients discontinued treatment and among these 4 developed severe infections.

All previous reports have outlined the feasibility of antiviral treatment of patients with a decompensated cirrhosis, allowed to further refine selection of these patients (treatment unsafe for CTP ≥ 10), and established the relative safety of current schedules of treatment, providing that administration of cytokines could maintain safe levels of hemoglobin (> 10 g/dL) and of neutrophils (> 750/dL). Scant data are available on the impact of therapy on “long term” disease progression, avoidance of transplantation, and improvement of life expectancy. These hard clinical end points are particularly applicable to patients with advanced disease, as liver function is more likely to deteriorate within a few years in these subjects. Achieving HCV clearance has been clearly correlated with improved liver function, as apparent from significant reductions in CTP and MELD scores after treatment.[34] A standardized mortality rate analysis reported a lower liver-related mortality among cirrhotics with SVR (0.6: CI: 0.0-3.1) than in untreated patients[36]. Further benefits after HCV eradication and partial recovery of liver metabolic activity were no more allograft failure secondary to recurrence of viral infection[37], and eventually long term removal of those patients who cleared HCV-RNA from the waiting list for liver transplant. We have reported a significant improvement in overall and event-free survivals as well as in clinical status and laboratory profile of patients who eventually cleared HCV after treatment with Peg-IFN alpha-2b and ribavirin administered for 24 wk. During the follow-up, the total number of decompensated events was significantly higher in controls and non-responders as compared with patients who achieved a SVR.

CONCLUSION

The main goals of treating cirrhotic patients are to attain SVR, halt disease progression, and prevent re-infection of the liver graft. Antiviral therapy for patients with chronic hepatitis C and an advanced stage of compensated or decompensated liver cirrhosis, is evolving: If left untreated, cirrhosis due to chronic HCV infection, is associated with decreased survival, whereas current data from existing trials suggest a reduction in the complication for those with an SVR. As in patients with milder liver disease, standard schedules of treatment may be efficacious particularly for those harboring HCV genotype 2 and 3 infection, in which HCV-RNA is rendered negative during treatment in more than half of individuals. Conversely, the risk-benefit ratio of treating patients with genotype 1 infection remains to be defined. Liberal use of hematopoietic cytokines will either enable the recipient to tolerate full dosage and course of treatment and prevent development of treatment-associated infections. Therapy is inadvisable for individuals with poor hepatic reserve. Although response rates appear to be lower in cirrhotic patients with and without complications of liver disease, successful antiviral therapy is potentially lifesaving.

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