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Antiviral therapy in patients with HCV-cirrhosis

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ABSTRACT

The main cause of liver cirrhosis and liver cancer in the western world is Hepatitis C virus (HCV) infection. Liver transplantation is the only effective treatment once the disease is decompensated. In viremic patients who undergo transplantation, disease recurrence is universal resulting in the development of a new cirrhosis in about one third of the patients after 5 to 10 years of follow-up. Initiation of the antiviral treatment with Peg-IFN and ribavirin prior to transplantation may prevent HCV recurrence if a sustained viral response (SVR) is achieved. Moreover, it might even be possible to achieve an improvement of the liver function degree so that transplantation may be differed.

There are few studies that assess the efficacy and safety of the antiviral treatment in the cirrhotic setting. Available information shows SVR rates between 20 and 40%, lower with decompensated disease. The need for treatment withdrawal and dose reductions is significant in this setting. Cytopenias are one of the most frequent adverse effects; hematopoietic growth factors have shown to increase patient compliance, but it is still unclear whether they result in greater SVR. In addition, an increased risk of bacterial infections has been recently described, with a recommendation to use prophylactic therapy during antiviral treatment. In conclusion, antiviral therapy is an option for cirrhotic patients who have a good liver function but should not be recommended in patients with Child-Pugh-Turcotte class C, due to a high risk of severe complications.

Key words. Liver cirrhosis. Liver cancer. Hepatitis C virus. Liver transplantation.

INTRODUCTION

Hepatitis C virus (HCV) infection is the main cause of liver cirrhosis and liver cancer in the western world. Once the cirrhosis has developed, survival at 5 years decreases below 50%. For this reason, when a cirrhotic patient shows signs[1] of disease decompensation, the only effective treatment is liver transplantation. Indeed, HCV cirrhosis and its complications have become now the indication of nearly 50% of liver transplantations performed in developed countries.

Unfortunately, if viral infection is not eradicated prior to the surgery, HCV recurrence in the recipient is the rule, resulting in the development of graft cirrhosis in a high proportion of liver recipients (20 to 30%) in a period of about 5 to 10 years from surgery.[2-3] Recurrence of the original disease is one of the causes of the poorer graft and patient survival observed in HCV liver recipients compared to other etiologies.[4]

Several studies have shown an association between pre-transplantation viral load and post-transplantation outcome.[5] It has hence been hypothesized that an aggressive antiviral approach prior to surgery, with reduction and/or inhibition of viral replication prior to transplantation may modify the disease natural history in the graft. This fact though remains to be confirmed.

The aim of HCV infection treatment in the cirrhotic setting is double: first, to eradicate HCV and in doing so, to prevent the recurrence of the infection; second, to improve the liver function in order to delay or avoid the need for transplantation.[6]

Treatment of the HCV-infected cirrhotic patient

Currently, the existing clinical guidelines do not recommend to initiate antiviral treatment in patients with end stage liver disease. However, when a sustai-

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ned viral response (SVR) is achieved, antiviral therapy has shown to offer several clinical benefits,[7] including improvement in the stage of fibrosis, decrease in the number of clinical decompensations, and prevention of the graft reinfection after transplantation.

The main limitation to treat patients with advanced liver disease is the frequent occurrence of side effects, particularly those related to cytopenias. Indeed, antiviral therapy typically worsens pre-existing cytopenias, which are very common in these patients.[7]

SVR in HCV related compensated cirrhosis (Table 1)

Cirrhosis is compensated when the hepatic synthetic function is preserved (albumin levels greater than 3.4 g/dL, total bilirubin less than 1.6 mg/dL, and prothrombin time or international normalised ration less than 1.6) and there is an absence of clinical decompensation, including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal hemorrhage or hepatorrenal syndrome.

Two large clinical studies have assessed through a post-hoc analysis the efficacy of antiviral treatment in patients with compensated cirrhosis.[8,9] Both studies included only patients categorized as Child-Pugh-Turcotte (CPT) class A. In one of them[8] an SVR rate of 43% at week 48 was achieved. Patients were treated with pegylated interferon (Peg-IFN) alpha 2a and ribavirin 1000-1200 mg/day. In the second study[9] with Peg-IFN alpha 2b 1,5 μg/kg once weekly and ribavirin 800 mg/day, a similar rate was achieved (SVR of 44%).

Previous studies did not differentiate patients with cirrhosis from those with bridging-fibrosis (F3), so that was not possible to estimate the response in the subgroup of cirrhotic patients.

In a recent Italian study,[10] in which only patients with compensated cirrhosis and portal hypertension were included, treatment was administered for one year at doses of Peg-IFN alfa 2b 1 µg/kg weekly plus ribavirin 800 mg/day. An SVR was achieved in 22% of patients, significantly lower in those infected with genotypes 1 and 4 (13%) compared to genotypes 2 and 3 (83%).

SVR in HCV-related decompensated cirrhosis (Table 2)

Due to the potential severity of adverse effects, classically antiviral treatment was not recommended in patients with decompensated cirrhosis. Most patients who have had a first episode of clinical decompensation though, maintain a reasonably stable degree of liver function after the resolution of the acute episode, so that they could potentially remain

Table 1. Treatment of compensated cirrhosis.

Author, yr (n)	IFN	RBV (mg/d)	SVR (%)	G 1-4 (%)	G 2-3 (%)
Marrache 05 (32)	Peg 2b (1,5 ug)	800-1200	36	21	61
Heathcote 00 (80)	Peg 2a (180 ug)	-	30	12	51
Di Marco 07 (51)	Peg 2b (1 ug)	800	30	23	83
Everson 08 (68)	Peg 2a (180 ug)	-	37	NA	NA
Syed 08 (104)	Peg 2b (1 ug)	800	35	13	60
Roffi 08 (56)	Peg 2b (1 ug)	800-1200	40	28	80

SVR: Sustained Viral Response. **IFN:** Interferon. **RBV:** Ribavirin. **G:** Genotype. **d:** day. **NA:** Not Available.

Table 2. Treatment of decompensated cirrhosis

Autor (n)	IFN (+ RBV)	Child	SVR G 1-4 (%)	G 2-3 (%)
Crippin 02 (15)	IFN	C	0	0
Thomas 03 (20)	IFN	C	2 (10)	2 (100)
Forns 03 (30)	IFN	A-C	3 (12)	3 (60)
Everson 05 (124)	IFN	A-C	11 (13)	19 (50)
Iacobellis 07 (66)	Peg 2b (1)	B/C	3 (7)	10 (43)
Tekin 08 (20)	Peg2a (135)	A/B	6 (30)	NA
Carrion 09 (51)	Peg 2a	A-C	1 (4)	9 (40)
Iacobellis 09 (94)	Peg 2b (1.5)	A/B	8 (16)	25 (57)

SVR: Sustained viral response. **IFN:** Interferon. **RBV:** Ribavirin. **G:** Genotype. **d:** day. **NA:** Not available.

good candidates for antiviral treatment. It is expected that tolerance would be worse in this setting.

There are only a few studies reporting single center experiences with small number of patients included whose aim has been to assess the efficacy of antiviral treatment in patients with decompensated cirrhosis.[6,11-16] Although doses and treatment durations differ in published series, results are similar both in terms of virological response and SVR post-transplantation. The data though is not robust enough so as to draw consistent conclusions.

In 2003, the International Liver Transplantation Society published an HCV treatment guideline in which the Experts Committee recommended the utilization of IFN in patients with a CPT score below 7 or MELD score below 18, considered its use in patients with CPT score between 8-11 or MELD score between 18-25 and did not recommend treatment for patients with CPT score above 11 or MELD over 25.[17]

The first study on antiviral therapy in patients with decompensated cirrhosis was an American pilot study[14] in which the tolerance to increasing dosage of antiviral drugs was tested. Fifteen patients were included, 3 were treated with IFN alpha-2b (1 MU/day), 6 with IFN alpha-2b (3 MU thrice weekly), and 3 with IFN alpha-2b (1 MU/day plus ribavirin, 800 mg twice daily). About one third (33%) of the patients achieved a complete viral clearance at end of treatment, while another 55% achieved a marked decrease of viremia. However, the number of severe adverse effects reported during treatment was high, and the study had to be prematurely discontinued.

In a later study,[11] a therapeutic approach named slow accelerating dose was used; antiviral treatment was started at low doses (Peg-IFN alpha 2b 0.5 μg/kg/week or Peg-IFN alpha 2a 90 μg/week plus ribavirin 400 mg/daily). Dosage was reassessed every two weeks in order to reach progressively the optimum dose. A complete end-of-treatment response was achieved in 39% of patients, but only 21% obtained an SVR (11% genotype 1, 50% genotypes 2-3). All the patients with SVR that underwent liver transplantation remained free of viral recurrence at the end of the study.

Recently, an Italian study included 66 patients treated with Peg-IFN alpha 2b (1 μg/kg/week) plus ribavirin at a standard dosage for 24 weeks. An SVR of 20% was achieved.[12] All patients with a CPT score under 10 tolerated the treatment without developing severe adverse effects. The same authors published this year[16] a new study in which 94 patients with decompensated cirrhosis and a CPT score below 9 were included. Treatment dosage used was the standard used in the non-cirrhotic setting (Peg-IFN alpha 2b 1.5 μg/kg/week + ribavirin 800-1000 mg/day during 24 weeks for genotypes 2 and 3 or Peg-IFN alpha 2b 1.5 μg/kg/week plus ribavirin 1000-1200 mg/day during 48 weeks for genotypes 1 and 4). An SVR of 35% was achieved (16% for genotype 1 and 60% for genotypes 2-3). Sixty per cent of patients tolerated full doses, but about 20% had to discontinue treatment due to severe adverse effects.

A recent Spanish study[15] included 102 patients in two groups matched by age, sex and CTP score. One of the groups received treatment with pegIFN alpha 2a (180 μg/week) plus ribavirin (doses adjusted to renal function). Patients with marked cytopenias (hemoglobin < 10 g/dL, platelets < 30000 or neutrophiles < 900) were excluded. Mean treatment duration was 15 weeks. In 24 patients (47%) HCV-RNA became undetectable. Out of these 24, 9 did not maintain the viral response by the time they underwent transplantation, so that the response rate decreased to 29%. After the surgery, HCV infection recurred in 5 of the remaining patients. Overall, 20% of the treated group achieved an SVR post-transplantation. Importantly, none of the patients with CPT class C obtained an SVR.

Effect of antiviral therapy on liver synthetic function

There is very little information about the effects of antiviral treatment on liver function and disease complications. If liver synthetic function was improved, one would anticipate a delay in the need for liver transplantation as well as an increased survival in those not candidates for transplantation. Indeed, the accumulated experience with patients with HBV-related cirrhosis is that viral suppression with the use of nucleos(t)ides induces a marked improvement in liver function and reduces the number of clinically relevant complication events.[18-21]

A Japanese study dating from 2002 in which the standardized mortality rate among cirrhotics was analyzed showed that patients who achieved an SVR presented a reduction in liver disease mortality.[22]

The achievement of an SVR is a requirement in order to obtain a real improvement in liver function.[12] Patients who are not able to maintain the viral response over prolonged periods of time do not improve significantly their liver function tests.[11] In the 2007 study by Di Marco, *et al.*,[10] only 6% of patients who achieved an SVR developed a worsening of their liver disease as opposed to 38% among non responders. In the 2007 study by Iacobellis, *et al.*,[12] a significant re-

duction in the decompensation event incidence was noted among patients who were under treatment, regardless of whether they had obtained an SVR. Despite this, there were no significant survival differences between those treated and the control group. However, a post hoc analysis showed a survival benefit for those achieving an SVR. CPT score worsened in patients who did not clear the virus. In the recent spanish study by Carrión, et al.,[15] the authors showed that during the treatment period, both the rate of decompensation as well as survival were similar in the treatment and the control groups. ALT levels decreased in treated patients and remained stable in the control group. CPT and MELD scores worsened significantly in the treatment group, potentially due to concomitant antiviral drug-related reasons such as hemolysis (increase in bilirrubin levels) or anorexia (decrease in albumin levels).

Effect of antiviral therapy on liver fibrosis

Several research lines support the theory that liver fibrosis is not a static unchangeable state and it is rather a dynamic process at least partially reversible.[24,25] In one study, patients who achieved an SVR presented an improved histologic index, with a reduction of the fibrosis score of -0.88 U/year after 3 years of follow-up.[26] A post hoc analysis of a clinical trial that enrolled 3010 patients detected an improvement in the histologic indexes in 50% of responders. Moreover, a complete cirrhosis resolution was reported in 8% of patients.[24] Together with the amelioration of the necro-inflammatory activity, the improvement in the stage of fibrosis may explain the portal haemodynamic changes that are detected in sustained responders, changes that in turn might explain the decreased number of decompensation events observed in these patients. In a study by Rincón, *et al.*,[28] patients under antiviral[27] treatment presented a significant decrease of portal pressure compared with controls.

Management of antiviral treatment related cytopenias

The development of severe cytopenias during antiviral treatment is a major limitation, especially in cirrhotic patients who tend to present lower counts of the three blood lineages. IFN causes pancytopenia due to bone marrow production suppression.[22] Granulocyte and lymphocyte counts may decrease between 30 to 50% from baseline values.[29]

IFN-related leucopenia occurs in about 20% of treated patients.[30] It is managed with dose reduction or drug withdrawal, thereby reducing the chances to obtain an SVR. Utilization of growth factors such as G-CSF or filgastrim, at a weekly scheduled dose of 300 ìg, can correct the IFN reduced leucopenia, allowing patients to maintain full doses.[31]

Treatment-related anemia is due to IFN-induced erithrocyte production in the bone marrow together with ribavirin-induced dose-dependant hemolytic anemia.[29] Anemia usually peaks during the first twelve weeks of treatment. Unfortunately, ribavirin dose reduction below 80% of the optimal dosage during the first twelve weeks hinders the possibilities to achieve an early viral response (EVR), the best predictor of SVR.[32]

Current guidelines recommend ribavirin dose reduction to 600 mg/day when hemoglobin value falls below 10 g/dL, and drug withdrawal when hemoglobin falls below 8.5 g/dL. In patients under antiviral treatment, increased serum levels of erithropoetin can be found, but this physiological elevation is not sufficient to compensate the anemia-producing mechanisms.[33] The use of human recombinant erithropoetin (EPO) at a dose of 10,000-30,0000 UI / weekly may be useful in this setting; 88% of patients receiving EPO versus 60% of control patients are able to maintain optimal dose of ribavirin.[34]

The management of trombopenia is based on interferon dose reductions. There is a pilot study with eltrombopag, a trombopoetin receptor agonist, in cirrhotic patients under antiviral treatment. Seventy-four patients with a platelet count between 20,000 and 70,000 were randomized in four branches, and they were given placebo or 30, 50 or 75 mg of eltrombopag respectively. Most patients (75-95%: higher proportion as higher was the dose of eltrombopag) achieved platelet counts above 100,000 after 4 weeks of treatment, and could therefore start antiviral treatment. After 12 weeks of treatment, IFN initial dose was maintained in 35-65% of patients treated with eltrombopag compared to only 6% of those under placebo.[34]

Antiviral treatment and risk for infections

One of the main disadvantages of IFN treatment is the risk for development bacterial infections, as previously reported in patients with HBV-cirrhosis.[35]

A similar trend was observed in the study by Everson, *et al.*, in which numerous adverse clinical

events were reported during the treatment period.[11] Further studies have tried to elucidate whether these complications occur as part of the natural history of the disease or are due to the treatment itself.

IFN-induced neutropenia has been postulated as the main risk factor for the development of bacterial infections. Therefore, current practice guidelines do not recommend IFN use in patients with neutrophil counts below 1,500 cells/mL. Several small studies did not show an increased risk of severe bacterial infections in cirrhotic patients under antiviral treatment, even in those with marked neutropenia.[9,10] However, in the 2007 study by Iacobellis, *et al*.,[12] a statistically significant increased incidence of infections was observed in the treated group compared to the controls; infectious related mortality did not differ between groups. Poor liver reserve (CPT class C) and neutrophil count below 900 remained as independent risk factors associated with infection.

The study by Carrion, et al.[15] was designed to evaluate the safety of antiviral treatment. They carefully assessed the incidence of bacterial infections and clinical complications during the treatment period. 102 patients were enrolled, 51 were included in each group, matched by sex, age and CPT class. Clinical adverse effects were frequent during the treatment period. Forty-nine percent of patients required dosage adjustments, and 43% of patients required drug withdrawal due to viral non response, severe infection, clinical decompensation or severe trombopenia. Three controls and twelve treated patients developed bacterial infections, with spontaneous bacterial peritonitis (SBP) being the most common type of infection and Gram negative bacilli the main pathogenic agents. Five patients from the treatment group developed a septic shock, while this event was not reported in any patient from the control group. In the univariate analysis, poor liver function and low blood cells count were significantly associated with the risk of infection. In the multivariate analysis, independent factors associated with a high infection risk included antiviral treatment and CPT class B-C. Indeed, most of bacterial infections occurred in patients with a basal CPT score > 7 or MELD score > 14. Interesting, this study also showed that there were no differences in the risk for developing bacterial infections between patients from both groups who were under prophylactic treatment with norfloxacin.

DISCUSSION

In patients with HCV-related cirrhosis and positive viremia at the time of transplantation, disease recurrence in the allograft is the rule, resulting in the development of a new cirrhosis in about one third of the patients after 5 to 10 years of follow-up. Peg-IFN and ribavirin are the only therapeutic tools available to cure the infection. When antiviral treatment is initiated prior to transplantation and an SVR is achieved, HCV recurrence is prevented. In addition, liver function can improve, differing or even avoiding the need for transplantation.

Available studies in the cirrhotic setting have reported SVR rates between 20 and 40%, with a high proportion of treatment withdrawal and dose reduction. The Use of hematopoietic growth factors can improve treatment-induced cytopenias thereby increasing patient compliance. In patients with decompesated disease, a higher susceptibility for bacterial infections development, particularly SBP, has been described. This risk seems to diminish in patients under prophylaxis with norfloxacin. Treatment is not recommended in patients with CPT class C due to a high risk of severe complications.

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