Treatment of HCV infection in patients with cirrhosis

Angelo Alves de Mattos,* Ângelo Zambam de Mattos**

* Head Professor of the Department of Gastroenterology and of the Post-Graduate Course of Hepatology of
Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Brazil; President of the Latin American Association for the Study of the Liver.
** Gastroenterologist and Post-Graduate Student in Hepatology of Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Brazil.

ABSTRACT

The treatment of patients with cirrhosis has the following purposes: to prevent the complications of the disease; to allow for the regression of cirrhosis; and to prevent reinfection in the graft in patients undergoing liver transplantation. When the sustained viral response is evaluated in patients with cirrhosis, especially in those with decompensated disease, it is noted to be lower than that of patients with chronic hepatitis, and with a higher possibility of complications of the treatment. Based on a review of the literature, we conclude that we should treat patients with compensated cirrhosis, probably also those with portal hypertension, and patients with decompensated cirrhosis only when included on the transplant list, as long as Child B with HCV genotype 2 (possibly 3) and preferably after clinical compensation.

Key words. Cirrhosis. Peginterferon. Hepatitis C virus.

The latest guidelines of the AASLD considered patients with compensated cirrhosis as a formal indication for treatment of hepatitis C virus (HCV) and patients with decompensated cirrhosis as a special patients group provided that they are included on the liver transplantation list.[1]

Treatment of patients with cirrhosis would have three relevant points as a rationale: to prevent the complications of the disease; to allow for the regression of cirrhosis; and to prevent reinfection in the graft in patients undergoing live transplantation.[2]

A retrospective non-randomized study[3] evaluated the effect of sustained virological response (SVR) on clinical outcomes of patients with HCV and compensated cirrhosis. In 113 patients with Child-Turcotte-Pugh (CTP) Class A cirrhosis treated for hepatitis C, SVR was observed in 33%. In a mean 7.7-year follow-up, hepatocellular carcinoma (HCC) was diagnosed in 24/76 of those without SVR and in 1/37 of those with SVR (p=0.01). Mortality was 20/76 without SVR and 0/37 with SVR (p=0.002). Thus, it seems that the treatment provides a better progno-

sis in patients with SVR. Another study,[4] multicentric and retrospective, evaluating the role of SVR to interferon (IFN) in the evolution of HCV cirrhosis in a cohort of 920 patients (124 with SVR), with a mean 96.1-month follow-up, also found fewer complications, HCC and death in patients with SVR. However, considering the slow evolution of chronic HCV infection, it has been difficult to demonstrate the real benefit of therapy.[1] Trying to bring more light into the matter, it was published in this year a systematic review with meta-analysis aiming at determining the risk of HCC after treatment of HCV in cirrhotics. The authors find a significant reduction in the risk of developing the neoplasm in the group with SVR; results on treated *vs.* untreated patients was not sufficient to significantly prove benefit of the treatment when response was not considered; maintenance therapy with IFN in nonresponders did not show any advantage and is not recommended.[5]

With respect to the regression of cirrhosis, we understand the importance of the study of Mallet, *et al.*,[6] which evaluated 96 patients with cirrhosis (CTP-A), using as criterion of response when regression of fibrosis was greater than or equal to 2 points in the METAVIR classification. SVR was observed in 41% of this population, and 18 patients were reported to have undergone regression of cirrhosis (17 with SVR and 1 with biochemical response). In a 10-year follow-up, 35% showed at least one complication of the disease and 23% died or un-

Correspondence and reprint request: Dr. Angelo Alves de Mattos
Rua Coronel Aurelio Bitencourt 35/201, Bairro Rio Branco,
Porto Alegre, Brazil, 90430-080
E-mail is: angeloamattos@gmail.com

derwent liver transplantation, whereas those with regression of fibrosis did not show any relevant complication. The study concluded that patients treated for HCV may have regression of cirrhosis. However, it reiterates that patients with SVR and cirrhosis should be followed in order to prevent complications.

Recurrence of hepatitis C virus is universal after liver transplantation. This fact is important, as approximately 1/3 of cases develop cirrhosis in 5-10 years and patients treated with SVR show a significant decrease in virus recurrence.[7] In a study[8] in which 124 patients with decompensated cirrhosis were treated with a progressive regimen (IFN or PegIFN plus ribavirin), from those in which the PCR-HCV became negative, 80% remained with the same status after transplantation.

Despite the benefits of the treatment, when we evaluate studies related to patients with cirrhosis, we conclude that SVR, in general, is poorer and when patients have decompensated cirrhosis, the degree of evidence favoring treatment is smaller, both due to the minor response and the higher possibility of complications, making this recommendation at least debatable.

Everson, *et al.*,[9] examined predictors of response and assessed the impact of disease severity in SVR, based on data of patients from the HALT-C study.[9] This study counted with 1046 previously non-respondent patients with advanced fibrosis or cirrhosis and found SVR in 23% of those labeled as F3, with more than 125,000 platelets, and in 9% of those with cirrhosis, and less than 125,000 platelets (p < 0.0001). The presence of cirrhosis was the most important independent factor related to therapeutic response. The fact that fibrosis affects therapeutic response has been described over time in meta-analyses performed with randomized studies.[10] In a study[11] evaluating the treatment of 400 patients with IFN and ribavirin, we obtained 38% of SVR in F1 and F2 patients and 28% in F3 and F4 patients. Similarly, when evaluating another cohort of 323 patients,[12] all with HCV genotype 1 treated with PegIFN and ribavirin, SVR was of 52% in F1 and F2 patients whereas it was of 29% in F3 and F4 patients (p<0.01). In the logistic regression analysis, the fibrosis staging was an independent factor for response, and, when the diagnosis was cirrhosis, SVR was of 18.9%.

The use of PegIFN with ribavirin for 48 weeks in naïve patients with HCV in a cohort of 124 patients with advanced fibrosis or cirrhosis (CTP-A) resulted in an RVS: 52% X 38% (those with a ribavirin dose lower than 600-800 mg), p=0.153. In the

multivariate analysis, SVR was independently related to the genotype and to the platelets count. Treatment was discontinued in more than 20% of patients, which calls our attention to its side effects.[13] In another study[14] that evaluated 87 patients with compensated cirrhosis and 278 patients without cirrhosis, SVR was of 45.9% and 65.8% respectively. The authors suggested treatment also for the cirrhotic group, but stressed the need for caution due to the increased likelihood of side effects. A recent study of PegIFN and ribavirin in advanced fibrosis evaluated 341 genotype 1 or 4 patients (99 with advanced fibrosis) and 1547 genotype 2 or 3 (380 with advanced fibrosis) from 3 randomized international trials. It showed an SVR of 60% for patients without advanced fibrosis, 51% for those with bridging fibrosis and 33% for the ones with cirrhosis in genotype 1 or 4 cases (p<0,05). In genotype 2 or 3, it described an SVR of 76% for patients without advanced fibrosis, 61% for those with bridging fibrosis and 57% for the ones with cirrhosis (p<0,05). The authors concluded that patients without advanced fibrosis have a greater SVR, independently of genotypes, but it is important to state that SVR was not influenced by the degree of fibrosis when patients achieved RVR (or even complete EVR in the case of genotypes 1 or 4).[15]

When evaluating the treatment of patients with HCV cirrhosis, and with portal hypertension in a prospective, controlled and randomized study[16] with 102 patients (51 with 1 μg/kg PegIFN alpha-2b for 52 weeks and 51 with 1 μg/kg PegIFN alpha-2b + 800mg ribavirin), SVR was of 9.8% and 21.6% respectively (p = 0.06), and the multivariate analysis should that SVR was related to genotype, viral load and early virological response (EVR) with negative PCR-HCV. It is noteworthy that 33 patients discontinued treatment due to side effects. Patients with SVR had fewer complications during follow-up (6.2 X 38.3%, p = 0.03). Giannini, *et al.*,[17] when treating 85 patients with cirrhosis and portal hypertension with PegIFN and ribavirin (48% naïve) observed SVR in 26% (48% in patients with HCV genotype 2 and 33% in patients with HCV genotype 3), and, in the multivariate analysis, the independent factors of response were viral load, presence of genotype 2/3 and complete EVR. The presence of portal hypertension in this study was not associated with SVR. Clinical outcomes were noted to be better in patients with SVR.

The study of Rincon et al., is remarkable for showing that the treatment decreased the hepatic

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venous pressure gradient in patients with advanced fibrosis related to HCV.[18]

With respect to patients with decompensated cirrhosis, in 2003, the International Liver Transplantation Society recommended the use of IFN in patients with CTP equal or below 7 or MELD below 18; it considered the possibility of its use in those with CTP between 8 and 11 and MELD between 18 and 25 and contraindicated it in patients with CTP greater than 11 or MELD greater than 25.[19]

The first major study in the literature in this regard was published by Everson, et al.,[8] evaluated 124 patients with different degrees of liver dysfunction (45% with CTP A and others with CTP B/C), treated with IFN or PegIFN and ribavirin with a progressive regimen, and found SVR of 24% (13% in genotype 1 and 50% in genotypes other than 1). It should be noted that adverse effects were frequent. However, we remind that the work by Iacobellis, et al.,[20] had the greatest impact on the possibility of treating this patient population. In this study, 66 patients were treated for 24 weeks with PegIFN (reduced dose) and ribavirin and the results were compared with those of 63 untreated controls. Twenty seven patients tolerated the medication, 26 patients required dose reduction, and 13 patients discontinued therapy. SVR was of 43.5% in patients with HCV genotypes 2 and 3 and 7% in patients with HCV genotype 1 and 4. It is important to remind that, in treated patients, the odds ratio was 2.95 for severe infection and 1.97 for death. Despite these facts, the evolution of patients who responded to treatment in a 30-month follow-up was better than that observed in controls and non-responders. The same result was obtained when evaluating the survival of these patients. In conclusion, the study suggests treating patients CTP A/B with HCV genotype 2 (there was only 1 patient with HCV genotype 3).

When evaluating 20 patients with cirrhosis CTP A/B cirrhosis (30% were CTP A showing oesophageal variceal bleeding) also treated with a lower dose of PegIFN (all with HCV genotype 1), Tekin, et al.,[21] obtained an SVR of 30%. The authors suggest treatment with caution in CTP A/B with portal hypertension.

In a more recent study, Iacobellis, et al.,[22] treated 94 CTP A/B patients (already recovered from an episode of decompensation) with PegIFN and ribavirin in a conventional dose. Around 50% were CTP A (all with MELD ≤ 14) and there was no indication of which patients had HCV genotype 2 or 3, as they were merged into a single group. SVR was of 35.1% (16% in HCV genotype 1 and 56.8% in HCV genotype 2/3). From the group of patients with rapid virological response (RVR), 70.5% had SVR. The authors concluded that treatment of patients with HCV genotypes 2/3 and RVR should be continued as well as in patients with complete EVR and low viral load.

When evaluating patients waiting for liver transplantation in a study with a small number of cases (15 patients treated with PegIFN and ribavirin), 6 with HCV genotype 1, 7 with HCV genotype 2, and 2 with HCV genotype 3, classified as CTP greater than or equal to 9 and with a MELD score greater than or equal to 14, the SVR obtained was of 20% (43% in genotype 2 and 0% in genotype 1). All patients had side effects, so that the authors recommended a cautious treatment in this population and only suggested that it could be considered in patients with HCV genotype 2.[23]

With respect to genotyping as an important tool in the evaluation of treatment, it is important to consider the study in which 471 patients with naïve chronic hepatitis C (106 with cirrhosis) were treated with PegIFN and ribavirin (185 with HCV genotype 1, 157 with HCV genotype 2, 92 with HCV genotype 3, and 37 with HCV genotype 4). SVR was of 36% and 17% in those with genotype 1 and 4 respectively, considering the absence or presence of cirrhosis (p = 0.01); 79% and 33% in those with genotype 3 (p = 0.001); and 83% and 69% in those with genotype 2, (p = 0.1). Thus, the only group that did not show a statistically significant difference in SVR when evaluated the different degrees of fibrosis was that of patients with HCV genotype 2. In the multivariate analysis, the lack of response was related to the presence of cirrhosis and genotypes 1 and 4 of HCV.[24]

In another study evaluating the treatment of HCV in patients with chronic liver disease awaiting liver transplantation,[25] now a case-control study with 51 patients treated with PegIFN and ribavirin, SVR was of 20%. The response was also related to the presence of HCV with genotypes other than 1 and to the presence of RVR. It should be remarked that no patient with CTP C responded to therapy. In this work, it was observed a high incidence of infection related to the degree of hepatocellular dysfunction and treatment. It is interesting to note that they found a higher incidence of spontaneous bacterial peritonitis in patients without prophylaxis with norfloxacin. Despite possible methodological problems observed in the study, we should ponder whether or not antibiotic prophylaxis should be applied in this patient population.

Based on the literature review, we may conclude the following:

- Should we treat patients with compensated cirrhosis?

  Definitely.

- Should we treat patients with compensated cirrhosis and portal hypertension?

  Yes.

- Should we treat patients with decompensated cirrhosis?

  Only Child B patients listed for transplantation with HCV genotype 2.

  Only Child B patients after compensation (HCV genotype 2 and possibly 3).

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