

# Antiviral treatment for cirrhosis due to hepatitis C: a review

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**ABSTRACT** Chronic hepatitis C infection is an important cause of cirrhosis and hepatocellular carcinoma (HCC). Antiviral therapy (AVT) for patients with cirrhosis due to hepatitis C may retard the progression of cirrhosis and prevent both the development of HCC as well as the recurrence of hepatitis C following liver transplantation. This review highlights the issues associated with AVT for patients with compensated and decompensated cirrhosis due to hepatitis C virus.

Keywords: antiviral treatment, cirrhosis, hepatitis C  
Singapore Med J 2012; 53(4): 231–235

## INTRODUCTION

Chronic hepatitis C infection is a major cause of cirrhosis and hepatocellular carcinoma (HCC) in Western countries. Globally, an estimated 170 million individuals are chronically infected with hepatitis C virus (HCV) and 3–4 million persons newly infected annually.<sup>(1)</sup>

### Clinical profile

Chronic hepatitis C infection is a slow-progressing disease, with epidemiological studies showing that it takes nearly 20 years for the development of cirrhosis and 30 years for the development of HCC.<sup>(2–4)</sup> The occurrence of jaundice, ascites, coagulopathy or encephalopathy heralds the onset of decompensation in a patient with compensated cirrhosis. The annual risks for development of decompensation, hepatoma and death in patients with compensated cirrhosis due to HCV infection are reported to be 3.6%–6%, 1.4%–3.3% and 2.6%–4%, respectively.<sup>(5–8)</sup>

In India, as in many Asian countries including Singapore, where there are no standard screening programmes available, a sizeable proportion of patients with HCV infection are only detected following an episode of clinical decompensation and are hence not eligible for treatment. In a study by Sood et al, 182 (21.5%) out of 850 patients with HCV seen at a tertiary referral centre in North India over a ten-year period were ineligible for standard antiviral therapy (AVT), largely due to decompensated liver disease,<sup>(9)</sup> thus highlighting that cirrhotic patients form a significant proportion of those detected with chronic hepatitis C.

### Genotypes and quasispecies

HCV has an inherently high mutational rate that results in considerable heterogeneity throughout the genome. HCV is classified into four hierarchical levels, which include genotypes, subtypes/subgenotypes, isolates and quasispecies. HCV appears to simultaneously exist within an individual as a series of related but immunologically distinct variants called quasispecies, the

existence of which may provide the virus with a mechanism to escape the host immune response.<sup>(10)</sup> There are four major HCV genotypes (G1–G4), although genotypes 5 (G5) and 6 (G6) have also been described.

### Antiviral therapy

The primary goal of therapy for HCV infection is the eradication of virus, and thereby the prevention of liver-related deaths due to the development of decompensated cirrhosis and HCC. Sustained virological response (SVR) – the absence of detectable virus in blood 24 weeks after the completion of therapy – is an excellent surrogate marker for the resolution of HCV infection. Treatment response can also be predicted by using milestones such as rapid virological response (undetectable serum HCV RNA or at least a 2 log<sub>10</sub> decline in HCV RNA levels from baseline at week 4 of treatment), early virological response (EVR; undetectable serum HCV RNA or at least a 2 log<sub>10</sub> decline in HCV RNA levels from baseline at week 12 of treatment) and end of treatment response (undetectable serum HCV RNA at the end of treatment).

Therapy for chronic hepatitis C has evolved much since the introduction of interferons (IFNs). Longer-acting pegylated formulations of IFNs (PEGIFN) and the oral guanosine analogue ribavirin (RBV) are the current standard of care, and treatment with these achieves an SVR of about 42%–52% for G1-infected patients and 70%–80% for G2 or G3-infected patients with chronic hepatitis C.<sup>(11–18)</sup> Liver transplantation (LT) remains the definitive treatment for decompensated liver disease due to HCV. In fact, decompensated cirrhosis due to HCV accounted for 30%–50% of the transplants performed in the United States and Europe in 2005.<sup>(19,20)</sup> However, recurrence of HCV after LT is universal<sup>(21)</sup> and follows a more aggressive course than *de novo* HCV infection.<sup>(22,23)</sup> Indeed, patient and graft survivals are lower for patients receiving transplants due to HCV-related cirrhosis than due to other indications.<sup>(23)</sup>

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This review, which highlights the management of HCV in patients with liver cirrhosis, is based on a detailed search of the literature on the PubMed for related studies.

## ANTIVIRAL THERAPY IN PATIENTS WITH LIVER CIRRHOSIS

Cirrhosis is defined when there is progressive diffuse fibrosis along with the development of regenerative nodules.<sup>(24)</sup> The Child-Pugh score (or Child-Turcotte-Pugh score) is used to assess the prognosis of chronic liver disease, mainly cirrhosis, and is based on five clinical measures of liver disease – total bilirubin, serum albumin (S-albumin), international normalised ratio for prothrombin time (INR), ascites and hepatic encephalopathy. Similarly, the Model for End-Stage Liver Disease (MELD) score, a scoring system for assessing the severity of chronic liver disease, is computed based on serum bilirubin (S-bilirubin), serum creatinine (S-creatinine) and INR.<sup>(25)</sup>

### Compensated cirrhosis

Patients without clinical signs of decompensation and a Child-Pugh score < 7 are said to have compensated cirrhosis.<sup>(26)</sup> It is often difficult to label a patient as having compensated cirrhosis, as there are only subtle changes in liver parameters (e.g. albumin/globulin reversal and slightly elevated bilirubin levels). Ultrasonograms may show coarse liver echoes with surface nodularity and irregular margins, changes that are consistent with the development of cirrhosis. A liver biopsy may be needed when the clinical, laboratory and imaging parameters are normal or equivocal.

The ultimate goal of therapy for patients with compensated cirrhosis would be to prevent the development of decompensation and HCC, for which SVR is an excellent surrogate marker. Achieving SVR has been shown to prevent the progression of disease by regression of fibrosis,<sup>(27)</sup> reduction in portal hypertension<sup>(28)</sup> and decreasing the risk for development of HCC.<sup>(29,30)</sup> Registration trials for AVT in patients with chronic hepatitis C infection have included subsets of patients with advanced fibrosis and compensated cirrhosis (proved by liver biopsy). The SVR rates (for both advanced fibrosis and compensated cirrhosis) were 5%–10% for IFN monotherapy (3 million units [MU] thrice weekly [tiw] for 24 weeks) and 50% (G1: 41%; G2/G3: 73%) for PEGIFN  $\alpha$ -2a (180  $\mu$ g/week plus RBV 1–1.2 g/day for 48 weeks).<sup>(11-18,27)</sup>

According to a technical review by the American Gastroenterological Association,<sup>(31)</sup> patients with compensated liver disease due to HCV infection should be treated according to standard protocols, provided S-albumin is > 3.4 g/dl, S-bilirubin < 1.5 mg/dl, INR < 1.5, platelet count > 75,000/mm<sup>3</sup>, haemoglobin (Hb) > 12/13 g/dl (males 12 g/dl; females 13 g/dl) and S-creatinine < 1.5 mg/dl. However, the SVR is generally lower and adverse events necessitating dose reductions are higher (and more so for PEGIFN than standard IFN) in patients with cirrhosis compared to those without cirrhosis.

**Table 1. Recommendations for antiviral treatment in patients with HCV-related cirrhosis based on Child-Pugh and MELD scores.**

Recommendation for treatment	Child-Pugh score	MELD score
Strongly consider	≤ 7	≤ 18
In select cases	8–11	19–25
Treatment not advised	> 11	> 25

HCV: hepatitis C virus; MELD: Model for End-Stage Liver Disease score<sup>(25)</sup>

### Decompensated cirrhosis

There are no firm guidelines on AVT for HCV-infected patients with decompensated cirrhosis. According to the practice guidelines of the American Association for the Study of Liver Diseases,<sup>(32)</sup> a patient should be listed for LT with the onset of clinical decompensation. However, LT as a treatment option is less viable in developing countries due to both financial constraints and the non-availability of cadaver donors. The recommendations of the International Liver Transplantation Society Expert Panel on LT and HCV<sup>(33)</sup> for the treatment of HCV in patients with cirrhosis, based on the Child-Pugh and MELD<sup>(25)</sup> scores, are provided in Table 1.

For patients with decompensated cirrhosis (Child-Pugh class B/C), AVT may be initiated at a low dose, with frequent monitoring for adverse events.<sup>(32)</sup> Growth factors (GFs) may be instituted for those with dose-limiting side effects. In patients with decompensated cirrhosis, the aim of AVT is to improve health-related quality of life, decrease risks of HCC development, prevent further liver decompensation, retard the progression of portal hypertension, obviate or delay the need for LT (especially in countries where it is not widely available) and prevent post-transplant HCV recurrence (for patients listed for transplantation).

### Clinical trials

Table II summarises the published trials on AVT for patients with HCV infection and decompensated cirrhosis.<sup>(34-41)</sup> In general, trials have included patients on the LT waiting list with marginal cell counts and liver biochemistries (platelets > 35,000 cells/mm<sup>3</sup>; absolute neutrophil count (ANC) > 1,200 cells/mm<sup>3</sup>; Hb > 9 g/dl; S-creatinine < 1.5 mg/dl; INR < 2.5; S-albumin > 2.5 g/dl; S-bilirubin < 4 mg/dl). In trials involving patients with decompensated cirrhosis, SVR was defined according to standard definitions or HCV RNA negative after transplantation or at last measurement.

Crippin et al were the first to publish their experience of treating patients with HCV-related decompensated cirrhosis.<sup>(34)</sup> They enrolled patients on the LT waiting list with a high probability of transplantation within 12 weeks of enrolment in the study. The overall response rate during treatment (defined as a loss of HCV RNA by polymerase chain reaction [PCR]) was five (33%) patients out of 15. Two patients who underwent LT were HCV RNA positive by PCR at the time of transplant and both had HCV recurrence post-LT. The study was terminated early due to a high rate of adverse events (87%). There was one death due to empyema. The authors concluded that AVT was poorly tolerated

**Table II. Summary of trials on antiviral therapy for HCV-infected patients with decompensated cirrhosis.**

Study (year)	No. of patients	Child-Pugh class	Antiviral regimen	SVR No. (%)		Growth factors	Adverse events* (%)
				G1/4	G2/3		
Crippin et al <sup>(34)</sup> (2002)	15	C	I-2b ± R	0	0	No	87
Thomas et al <sup>(35)</sup> (2003)	20	C	I-2b	2 (10)	2 (100)	Yes	15
Forns et al <sup>(36)</sup> (2003)	30	A-C	I-2b + R	3 (12)	3 (60)	Yes	63
Everson et al <sup>(37)</sup> (2005)	124	A-C	I-2b + R; PI-2b + R	11 (13)	19 (50)	Yes	24
Iacobellis et al <sup>(38)</sup> (2007)	66	B/C	PI-2b + R	3 (7)	10 (43)	Yes	59
Tekin et al <sup>(39)</sup> (2008)	20	A/B	PI-2a + R	6 (30)	NA	Yes	40
Carrión et al <sup>(40)</sup> (2009)	51	A-C	PI-2a + R	1 (4)	9 (40)	Yes	43
Iacobellis et al <sup>(41)</sup> (2009)	94	A/B	PI-2b + R	8 (16)	25 (57)	Yes	19.1

\*Events that caused either dosage reduction or the discontinuation of treatment.

HCV: hepatitis C virus; SVR: sustained virological response; G1-4: HCV genotypes 1-4; I-2b: interferon  $\alpha$  2b; PI-2b: pegylated interferon  $\alpha$  2b; PI-2a: pegylated interferon  $\alpha$  2a; R: ribavirin; NA: not available

in this group of patients and is of limited use in the pre-transplant setting. However, although the reported rate of adverse events was high, a majority of these were dose-related cytopenias rather than infectious complications.

Thomas et al studied 27 patients on the LT waiting list, of whom 20 patients were found to be eligible (seven patients were excluded due to thrombocytopenia).<sup>(35)</sup> Pre-LT viral clearance was achieved for 12 patients among those eligible, out of whom four remained free of HCV post-LT. There were no deaths, infections or other side effects that required hospitalisation. However, all patients required GFs (granulocyte-colony stimulating factor [G-CSF]), the latter obviating the need for dose reductions. The authors concluded that AVT was a viable option for preventing post-LT HCV recurrence.

Forns et al studied the efficacy of AVT in patients enlisted for LT (expected waiting time < 4 months).<sup>(36)</sup> Of the 50 patients on the waiting list, 30 were found to be eligible and nine were HCV RNA negative by qualitative PCR. All patients were transplanted, but post-LT HCV recurrence was seen in only three patients. The significant predictors of virological response were lower pre-treatment viral load and a positive RVR. GFs were used and there were no deaths attributable to therapy. The authors concluded that with careful monitoring for adverse events and the use of GFs, AVT was a safe option.

Everson et al employed the low accelerating dose regimen (LADR) protocol for AVT in a cohort of 124 decompensated cirrhotic patients.<sup>(37)</sup> The starting doses for IFN  $\alpha$ -2b, PEGIFN  $\alpha$ -2b and RBV were as follows: IFN  $\alpha$ -2b (1.5 MU tiw), PEGIFN  $\alpha$ -2b (0.5  $\mu$ g/kg/week) and RBV (600 mg/day; 400 mg/day for patients with creatinine clearance < 50 ml/minute). Adjustments were gradually made (every two weeks) to try to reach maximally tolerated or standard target doses. The benefits of using LADR included enhanced patient adherence to treatment and earlier detection of side effects at a milder stage, when appropriate interventions could be made. Of the 47 patients who underwent LT, 15 were HCV RNA negative and 32 were HCV RNA positive prior to LT. 12 (80%) of the 15 HCV RNA-negative patients remained negative six months after LT. However, all of the 32

HCV RNA-positive patients relapsed. No difference was observed in the virological responses of patients based on the Child-Pugh classes. Significant predictors of SVR were infection with non-G1 genotype and the ability of patients to tolerate the full dose and duration of treatment.

Iacobellis et al, in a case control study (66 patients and 63 controls), compared the effects of AVT on survival and clinical decompensation.<sup>(38)</sup> Although no survival benefits were found in the group of AVT-treated patients on the whole, improved survival was seen in patients achieving SVR on subgroup analysis. There was an increased risk of infection in the treated group (odd's ratio 2.95), with predictors of infection being Child-Pugh class C and neutropenia (< 900 cells/mm<sup>3</sup>). However, there was no difference in deaths due to infection in the treated group compared to the controls. The authors concluded that AVT was beneficial in patients with HCV-related decompensated cirrhosis, especially in those with Child-Pugh class B/C and a favourable genotype.

In other studies, Tekin et al<sup>(39)</sup> obtained SVR in six (30%) out of 20 cirrhotic patients with G1 HCV infection by using PEGIFN  $\alpha$ -2a. Therapy was continued beyond three months only if patients achieved EVR. Meanwhile, Carrión et al, in a case control study, found that 20% of patients remained HCV RNA negative six months after LT, while virus recurrence was universal among controls.<sup>(40)</sup> Non-G1 genotype and EVR were predictors of successful response. Patients not on norfloxacin prophylaxis had an increased incidence of spontaneous bacterial peritonitis and/or bacteraemia. Iacobellis et al, in their study, observed that G2/G3 genotypes, complete EVR and adherence to the full course and duration of therapy were predictors for successful SVR.<sup>(41)</sup>

### Cytopenias and growth factors

Patients with cirrhosis are more prone to adverse effects due to therapy. IFN, by virtue of its bone marrow suppression effects, is known to cause thrombocytopenia, neutropenia and anaemia. RBV can cause anaemia due to haemolysis as well as bone marrow suppression.<sup>(42)</sup> Treatment-related cytopenias are more common with PEGIFN than standard IFN. Also, pre-existing cytopenias may preclude treatment with IFN. Neutropenia, while on

treatment, may put the patient at risk for infections, which can be life-threatening at times. Thrombocytopenia and anaemia may cause bleeding episodes and exertional fatiguability. Cytopenias due to AVT can be managed by the use of either GFs or by dose reductions. GFs (G-CSF and/or erythropoietin [EPO]) were used in a majority of studies on patients with decompensated cirrhosis to enable the continuation of treatment without dose reduction.<sup>(35-41)</sup>

Current guidelines recommend RBV dose reduction to 600 mg/day for Hb < 10 g/dl and drug withdrawal for Hb < 8.5 g/dl. For EPO, there is no universal consensus regarding the dosage regimen. In general, EPO is started when there is a fall in Hb level by > 3 g/dl from baseline, when Hb < 8 g/dl or for patients with symptomatic anaemia. EPO is given in divided doses subcutaneously, with a maximum weekly dose of 40,000–60,000 U, with an aim of maintaining Hb > 11 g/dl.<sup>(43)</sup> Rapid rise in Hb levels may predispose patients to the risk of thromboembolic events.<sup>(43)</sup> According to manufacturer's recommendations, PEGIFN doses should be reduced for absolute neutrophil count (ANC) < 750/mm<sup>3</sup> and the drug withdrawn for ANC < 500/mm<sup>3</sup>. PEGIFN  $\alpha$ -2a should be reduced for platelet counts < 50,000/mm<sup>3</sup> and discontinued for platelet count < 25,000/mm<sup>3</sup>. For PEGIFN  $\alpha$ -2b, the drug is reduced for platelet count < 75,000/mm<sup>3</sup> and discontinued for platelet count < 50,000/mm<sup>3</sup>.

G-CSF can be started at a dose of 300  $\mu$ g and titrated with frequent monitoring of blood counts once neutropenia develops in order to continue AVT without dose reductions.<sup>(43)</sup> Common side effects include bone/muscle aches and nausea/vomiting. Side effects can be minimised with G-CSF either two days before or after IFN injections. The use of GFs enables optimum adherence to the treatment protocol without drug withdrawal/dose reduction, thus indirectly helping to achieve SVR.<sup>(44)</sup> Recently, an orally active thrombopoietin receptor agonist (eltrombopag) that stimulates thrombopoiesis was found to facilitate the initiation of AVT in patients with thrombocytopenia associated with HCV-related cirrhosis.<sup>(45)</sup>

### Dosing and duration of therapy

The LADR regimen has been recommended for patients with HCV infection and decompensated cirrhosis by the consensus development conference on HCV and LT.<sup>(33)</sup> Treatment when initiated includes: IFN  $\alpha$ -2b (1.5 MU tiw) with PEGIFN  $\alpha$ -2b (0.5  $\mu$ g/kg/week) or PEGIFN  $\alpha$ -2a (90  $\mu$ g/week) with RBV (600 mg/day). The dosage of IFN is first increased, depending on tolerance, to achieve full dose treatment within 2–4 weeks. RBV dosage is subsequently increased in increments of 200 mg every two weeks, based on tolerance, to achieve an estimated optimal effective dose of 10.6 mg/kg/day. Reported literature has so far not demonstrated any difference in efficacy between the two types of IFN regimen in patients with cirrhosis.

Complete blood counts and liver biochemistries are checked once in two weeks till dose stabilisation and then once every month. HCV RNA should be measured every three months. For patients who fail to respond to 12 weeks of treatment with at

least a 2 log<sub>10</sub> decrease in HCV RNA levels, treatment may be discontinued.

Expected duration of initial treatment after a patient achieves optimal doses of both IFN and RBV would be six months for the G2 and G3 genotypes and 12 months for the G1 genotype. However, relapse rates are higher, particularly for G1, because of an inability to achieve optimal doses of both IFN and RBV. If treatment is stopped and a relapse occurs, one might consider reinstatement of AVT. An alternative approach could be the continuation of AVT at the same dosage for patients with G1 with on-treatment viral clearance up to the time of LT. However, the impact of such an approach needs to be further assessed. Post-AVT, responders should be monitored for relapse. Also, screening for HCC, hepatitis B vaccination and alcohol abstinence are advised, in general, for all HCV-infected patients with cirrhosis. Non-responders to AVT must be given the standard care for ascites and portal hypertension.

### Future options

With the number of patients with HCV-related cirrhosis on the rise, there is a growing realisation of the importance of AVT for this group of patients. Newer oral antivirals (telaprevir and boceprevir) have also been developed that, when added to the current standard of care, have improved SVR.<sup>(46-48)</sup> However, the impact of these drugs on patients with cirrhosis is not yet established in the literature.

### CONCLUSION

Aggressive AVT is recommended for patients with HCV and compensated cirrhosis. Often, HCV infection in patients is recognised only after an episode of clinical decompensation. However, as only a fraction of patients with decompensated cirrhosis are eligible for treatment, therapy must be initiated for these patients early by experienced clinicians, with frequent monitoring of blood counts and liver biochemistries.

In HCV-infected patients with decompensated cirrhosis, AVT prevents further worsening of liver function and may improve survival in the subset of patients for whom SVR is achieved. Importantly, pre-LT clearance of HCV RNA reduces the risk of post-LT HCV recurrence. The low SVR generally seen in HCV-infected patients with decompensated cirrhosis is due to the predominance of the G1 genotype, the inability to achieve full dose and duration of therapy, complications related to cytopenias and the worsening of liver function. Judicious utilisation of GFs may help to avoid reductions in antiviral doses while also improving optimum dose adherence, thus enabling the continuation of treatment without dose reductions in these patients.

AVT must be stopped in the absence of EVR. The subgroup of patients most likely to benefit from AVT is those with Child-Pugh class A/B cirrhosis and G2/G3 infection, and a low viral load. However, it is not known whether AVT does effectively improve life expectancy and help to avoid LT. Therefore, there is a need for future trials, with larger numbers of patients, that will evaluate the efficacy of the PEGIFN and RBV combination, the importance

of the systematic use of G-CSF and EPO in improving SVR, maintenance therapy with IFN, as well as AVTs involving newer drugs.

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