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Treatment of chronic hepatitis C infection in cirrhotic patients

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Characteristics of prospective patients for treatment

Epidemiologic studies suggest that liver cirrhosis develops after 20 years of active infection with hepatitis C virus (HCV) and that hepatocarcinoma develops after about 30 years of active HCV infection.[1-6] Liver cirrhosis may be compensated, in which case clinical and biochemical deterioration is absent, or it may be decompensated, in which case progressive deterioration of liver function is evident. Annual rates of decompensation, hepatocarcinoma, and death in patients with decompensated cirrhosis are 3.6%–6%, 1.4%–3.3%, and 2.6%–4%, respectively. Once cirrhosis becomes decompensate, the survival rate in the subsequent five years is 50%.[7] The foregoing justifies recommending treatment for compensate cirrhotic patients with hepatitis C.

The safety and efficacy of treatment is acceptable for patients with a Child–Pugh (CP) score less than 7 or a model for end-stage liver disease (MELD) score less than 18 *(Table I)*.[8] Treatment of patients awaiting liver transplantation may be considered provided that it is administered by experienced clinical personnel and that strict vigilance for adverse effects is maintained.[9]

Liver biopsy

- Who does not need a biopsy?
- HCV + HTP = cirrhosis
- HCV + decompensate = cirrhosis
- In the absence of HTP stigmas, a liver biopsy is necessary to evaluate the grading and staging of liver disease with accuracy.
- Whether biopsies should be taken from patients with HCV genotypes 2 and 3 is controversial.
- Invasive procedures are only justified if they have the potential to improve the treatment or management of the patient, for example:
  - biopsy for identification of hepatocarcinoma in patients with a diagnosis of cirrhosis, or
  - endoscopy for identification of esophageal varices.
- The need to predict treatment responses and optimize treatments should be taken into account in deciding whether to take biopsies.

Table I. Proposed guide for the selection of HCV patients with cirrhosis for interferon therapy.[8]

Treatment recommendation	CP score	MELD score
Highly recommended	< 7	< 18
Recommended in selected cases	8–11	18–25
Not recommended	> 11	> 25

Treatment of patients with cirrhosis caused by HCV

Treatment of patients with decompensate liver cirrhosis

Treatment of patients with decompensate cirrhosis may be recommended, depending on the evidence. Existing studies of treatment of cases of decompensate liver cirrhosis were not controlled and consisted of small numbers of patients who had weak tolerances to treatment and very low responses. Treatment of decompensate patients with cirrhosis and hepatitis C should only be undertaken in clinical studies or by clinical personnel with experience in the management of complications and treatment of patients awaiting liver transplantation.

Treatment of patients with compensated liver cirrhosis

With standard interferon monotherapy, the sustained viral response (SVR) is 5%–15%. With pegylated interferon monotherapy, the SVR is 20%–30%. Histological improvement is evident in a significant proportion of patients treated with pegylated interferon alfa-2a (44% of patients at a dose rate of 90 μg/week and 54% of patients at a dose rate of 180 μg/week). Improvement of liver histology by pegylated interferon alfa-2a treatment was most frequent in virological responders, but it also occurred in nonresponders.[10] An SVR of 30%–40% is typical of treatment of cirrhosis patients with interfer-

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on plus ribavirin; an SVR of 40%–50% is typical of treatment with pegylated interferon plus ribavirin.[11,13] SVRs are lower in patients with HCV genotype 1 and high viral loads. Hadziyannis[13] reported the most favorable responses in patients with cirrhosis: 48 weeks of treatment with pegylated interferon alfa-2a plus ribavirin resulted in an SVR of 50% (41% in patients with HCV genotype 1 and 73% in patients with HCV genotypes 2 or 3). This study showed that in patients with HCV genotypes 2 or 3, a low dose of ribavirin (800 mg/day) for 24 weeks is as effective as a higher dose of ribavirin for a longer duration. In contrast, in patients with HCV genotype 1, 48 weeks of high doses of ribavirin (1000–1200 mg/day) are necessary to attain an SVR of 52%.

The following conclusions are made

- In cases of patients with HCV genotypes 2 or 3 who have compensated cirrhosis, pegylated interferon plus 800 mg ribavirin should be administered for 24 weeks.
- In cases of patients with HCV genotype 1 who have compensated cirrhosis, pegylated interferon plus 1000–1200 mg ribavirin should be administered for 48 weeks.
- Patients who exhibit an SVR have attenuated necroinflammation and fibrotic activities.
- Recurrent and nonresponding patients exhibit mild improvements in liver histology.

Follow-up of patients with cirrhosis and hepatitis C during treatment

The combination of pegylated interferon plus ribavirin is well tolerated by most patients with advanced liver disease who have not developed complications. However, pegylated interferon plus ribavirin treatment of such patients frequently results in neutropenia, thrombocytopenia, and anemia. The reduction of blood lymphocyte concentrations is more frequent with pegylated interferon treatment than with unpegylated interferon treatment.[10,12] Laboratory examinations and frequent medical evaluations are recommended to detect potential adverse effects of treatment, to adjust doses of drugs, and, if necessary, to administer growth factors (erythropoietin and GCSF (Granulocyte Cell Stimulating Factor)). Evaluations should be conducted every 2 weeks until biochemical parameters are stable, and monthly thereafter. Liver US (Ultrasonography) and AFP (Alpha-fetoprotein) for detection of possible hepatocarcinoma should be done every 6 months. In patients with cirrhosis, superior digestive endoscopy should be conducted to detect esophageal or gastric varices. If esophageal or gastric varices are detected, nonselective BB should be initiated as the primary prophylaxis against acute bleeding.

Maintenance treatment

The main objective of antiviral therapy is an SVR. As SVR only occurs in a small proportion of patients with cirrhosis, for most cirrhosis patients, the objectives of treatment are reduction of inflammation, stabilization of fibrosis, prevention of clinical deterioration and complications associated with portal hypertension, and reduction of the risk of hepatocarcinoma. It is suggested that the hepatic venous pressure gradient should be used to evaluate responses to treatment because it is a precise and objective index of the progression of fibrosis and cirrhosis.[13,14] Several studies have shown that patients with SVR have a greater reduction in necroinflammatory activity, fibrosis, and cirrhosis than patients who do not exhibit an SVR.[10,16]

Three studies were initiated to evaluate the efficacy of maintenance therapy with low doses of pegylated interferon

HALT-C (long-term antiviral treatment to prevent cirrhosis) is a multicenter USA study sponsored by the National Health Institute. The aim of the study is to evaluate the effect of pegylated interferon alfa on prevention of the progression of fibrosis and clinical decompensation.[17] In this study, the patient is initially offered pegylated interferon (180 μg/week plus ribavirin), and the virological response is evaluated in week 20. If the patient is positive for HCV RNA, he/she receives monotherapy with 90 μg/week of pegylated interferon alfa-2a for an additional 3.5 years. The results of this study have not been published yet.

COPILOT (colchicine *vs* long-term pegylated interferon) is a multicenter USA study on maintenance with pegylated interferon. In this study, nonresponders were eligible for antiviral treatment and were allocated at random to receive colchicine (placebo) or pegylated interferon alfa-2b (0.5 μg/week) for 4 years. Preliminary results (follow-up at year 2) indicate that patients treated with pegylated interferon have a greater survival rate free from adverse events ($p = 0.007$; 95 CI = 1.18–3.08%). Symptoms of portal hypertension (varicose bleeding and a CP score > 2) were less frequent in patients treated with pegylated interferon. A substudy of this trial showed that pegylated interferon treatment significantly reduced the hepatic venous pressure gradient.[18]

EPIC 3 (efficacy of peg interferon in hepatitis C) is a study in which patients are given pegylated interferon alfa-2b treatment or no treatment. Results are pending.

Recommendations on the usefulness and efficacy of maintenance therapy depend on the results of these three studies. At present, the best strategy for managing nonresponder patients with advanced fibrosis or cirrhosis is unknown. However, the consensus was that such patients should be offered maintenance therapy or, if this is not possible, treatment with low doses of pegylated interferon.

Interferon and the prevention of hepatocarcinoma

Available evidence suggests that interferon has a preventative effect on the appearance of the hepatocarcinoma associated with HCV-induced cirrhosis and that this effect is more pronounced in patients with SVRs.[21,23]

Recommendations of the consensus panel

Are patients with HCV liver cirrhosis prospects for treatment?

Patients with liver cirrhosis are prospects for treatment because there is an SVR in 40%–50% of treated cases and because interferon has an antifibrotic effect and probably reduces the incidence of hepatocellular carcinoma.

Evidence quality: 2

Is treatment of cirrhosis patients with Child–Pugh (OK) scores of A contraindicated?

There is no contraindication for treatment of patients with Child–Pugh scores of A. However, consensus was not reached on patients with Child–Pugh scores of B or C. However, it was agreed that this group of patients should be treated on an individual basis by experts in the field or according to research protocols.

Evidence quality: 2

Should liver biopsies be taken from patients with clinical cirrhosis?

Liver biopsies are not justified in cases of patients with clinical evidence of liver cirrhosis, as it may be inferred with precision.

Evidence quality: 3

What is the treatment of choice for cirrhotic patients?

At present, these patients should receive pegylated interferon plus ribavirin. The duration of treatment should be adjusted according to the HCV genotype present.

Evidence quality: 1

Follow-up visits of cirrhotic patients after treatment for chronic HCV infection

These should be individualized according to the evolution of treatment and the presence or absence of adverse effects.

Evidence quality: 3

Is it appropriate to offer maintenance treatment with interferon to cirrhotic patients?

At present, there is insufficient information to make a recommendation on maintenance therapy with pegylated interferon. Therefore, it is necessary to wait for the results of large-scale ongoing studies.

Does treatment with interferon reduce the risk of hepatocarcinoma?

There is sufficient information to indicate that treatment of patients with chronic HCV infection reduces the incidence of hepatocellular carcinoma.

Evidence quality: 2

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