Chronic viral hepatitis C: management update

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Abstract

THE MANAGEMENT OF CHRONIC VIRAL HEPATITIS C is evolving rapidly. Monotherapy with interferon, the accepted standard of treatment until recently, achieves only a modest sustained virological response rate of 15%. Combination treatment with alpha-2b interferon and ribavirin has been shown to increase sustained response rates to 40% in patients who have never been treated with interferon and to 50% in those who have relapsed following monotherapy with interferon. However, side effects, which have led to the discontinuation of combination treatment in a significant proportion of patients, must be carefully monitored. Treatment with interferon alpha-2b and ribavirin has now been approved in Canada, but the selection and monitoring of patients suitable for combination treatment requires special expertise. Although improvements in current therapeutic options may be possible with more frequent, higher doses or long-acting forms of interferon together with ribavirin, low sustained response rates (i.e., below 30%) for patients with hepatitis C virus genotype 1 emphasize the need for novel antiviral medications that will target the functional sites of the HCV genome.

Review

Synthèse

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Hepatitis C virus (HCV) is the most common of the recognized chronic hepatitis viruses in Canada and the United States[1] and is a major cause of cirrhosis and hepatocellular carcinoma. The prevalence of hepatitis C infection in Canada is estimated to be between 0.5% and 1.2%.[2,3] The disease often remains asymptomatic for prolonged periods, but cirrhosis may develop insidiously in 20%–30% of chronically infected individuals over a period of 20–30 years.[4–6] Hepatitis C related cirrhosis has become the leading indication for liver transplantation in many transplant centres in North America. There are no effective vaccines available for HCV.

Hepatitis C virus is a single-stranded RNA virus that belongs to the flaviviridae family.[7] The structural and functional proteins of the HCV genome have been well characterized over the past 10 years. Of the 6 major HCV genotypes, genotype 1 is the most common; genotypes 2 and 3 are found in approximately 10%–20% of patients with hepatitis C in North America. Novel antiviral agents that target the functional sites of HCV are currently being developed.[7] In this review we examine how the presently available agents have changed the management of patients with hepatitis C.

In the past, treatment was limited to monotherapy with various types of interferon (i.e., interferon alpha-2a, interferon alpha-2b and consensus interferon) that have similar immunomodulatory and antiviral effects. Monotherapy achieves viral clearance in only 15%–20%.[8,9] The nucleoside analogue ribavirin has recently been evaluated in combination with interferon alpha-2b, and this combination of antiviral agents has markedly improved the sustained virological response. The possible responses to antiviral therapy are defined in Table 1 and will be referred to throughout this review. Ribavirin as a single agent enhances a type-1 cytokine-mediated immune response but does not suppress viremia levels; when given in combination with interferon synergistic antiviral effects are seen (Fig. 1).[10]

Diagnosis of chronic viral hepatitis C

The most practical screening tests for hepatitis C virus antibodies are second-

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and third-generation enzyme immunoassays (Table 2). The presence of HCV antibodies is usually confirmed by a more specific recombinant immunoblot assay. All patients positive for HCV antibodies by enzyme immunoassay and positive or indeterminate by recombinant immunoblot assay should be tested for HCV RNA by qualitative polymerase chain reaction to confirm chronic infection. Failure to detect HCV RNA at this stage may be related to the sensitivity of the assay, intermittent viremia or degradation of HCV RNA after sampling, or it may mean that the test is actually negative. Only 10%–20% of patients with acute hepatitis C eventually clear HCV infection.[11–13] A negative polymerase chain reaction should therefore be repeated, especially if there are abnormal liver enzymes present. In immunocompromised patients anti-HCV antibodies by enzyme immunoassay may be absent despite viremia in up to 10% of patients,[14] and these patients should be tested primarily by polymerase chain reaction if there is clinical suspicion of HCV infection.

Table 1: Definitions of responses to antiviral therapy

Type of response	Definition
Biochemical	Normalization of alanine transaminase levels
Virological	Undetectable serum HCV RNA by qualitative polymerase chain reaction
Sustained	Response maintained for more than 6 months after treatment cessation
Nonresponse	Failure of alanine transaminase levels to return to normal or HCV RNA to clear during treatment
Relapse	Recurrence of HCV viremia after treatment

The viral genotype should be determined in patients undergoing combination antiviral treatment because treatment for patients with genotypes 2 and 3 can be shortened from 12 months to 6 months. The benefit of additional HCV RNA quantitation for the determination of treatment duration is not well defined; this test is therefore not routinely recommended at present. However, knowing the viral load does help to predict the likelihood of treatment response; a viral load $\geq 2 \times 10^6$ copies/mL is predictive of reduced treatment response rates, especially in patients with genotype 1.[15,16]

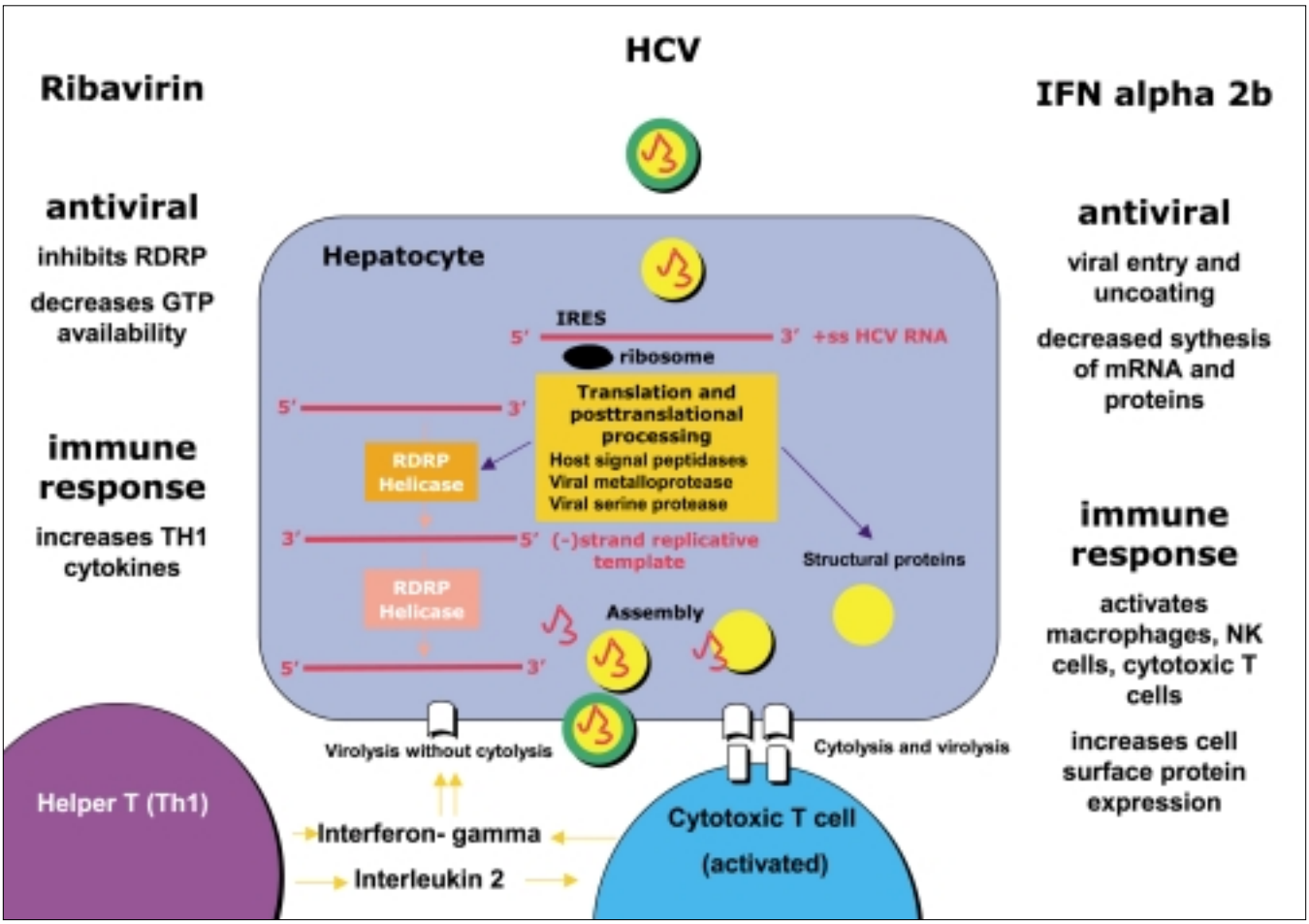

Fig. 1: Life cycle of hepatitis C virus in the hepatocyte and mechanism of action of alpha-2b interferon and ribavirin. HCV = hepatitis C virus, IRES = internal ribosomal entry site, RDRP = RNA-dependent RNA polymerase, + ss HCV RNA = positive sense single-stranded HCV RNA, NK cells = natural killer cells.

Assessment of patients with chronic viral hepatitis C

Patients with HCV infection should be assessed for the severity of chronic liver disease and for coexisting medical conditions.[17] Signs and symptoms of chronic liver disease and, in particular, decompensated liver disease (i.e., jaundice, ascites, encephalopathy or bleeding from esophageal or gastric varices) should be investigated. Patients with suspected advanced liver disease should be offered a gastroscopy to screen for esophageal varices.[18] If small varices are identified patients should be screened yearly, and if grade 2 or grade 3 varices are present a beta-blocker for the primary prevention of bleeding should be initiated.[18] Patients with cirrhosis should be offered screening for hepatocellular carcinoma.[19,20] However, the current screening methods, alpha-1 fetoprotein determination and ultrasound every 6 months, have sensitivities of only 50% and 70%, respectively, and curative therapy through resection or liver transplantation is possible in only a fraction of patients.[21] Patients with advanced or decompensated liver disease should be referred for an assessment for liver transplantation. Hepatitis C virtually always recurs after liver transplantation and may cause cirrhosis and loss of the hepatic allograft. Nevertheless, the short- and medium-term survival of up to 5 and 8 years, respectively, is similar to patients who receive a liver transplant for other reasons.[22–24]

Lifestyle risk factors such as alcohol consumption and intravenous drug use should be reviewed with patients. In particular, the need to abstain from alcohol use must be emphasized because alcohol is a significant risk factor for the progression of chronic viral hepatitis C. Patients at risk for recidivism should consider enrolling in a drug or alcohol rehabilitation program before antiviral treatment is initiated.[25–27] Coexisting viral, autoimmune, metabolic or drug-induced liver disease should be ruled out (Table 3). Patients should also be examined for extrahepatic manifestations of hepatitis C (e.g., porphyria cutana tarda or mixed essential cryoglobulinemia).

A liver biopsy is recommended for the majority of patients with elevated liver enzymes or clinical evidence of early cirrhosis. A biopsy will help to identify patients at higher risk for disease progression so they can be treated, as well as those with otherwise unrecognized coexisting liver disease.[28,29] In patients with normal alanine aminotransferase levels liver enzymes should be repeated at least 3 times in a 6-month period to ensure they remain normal and at least yearly thereafter.[30]

Management of patients with chronic hepatitis C

All patients should be informed of the natural progression of the disease, measures to prevent viral transmission and treatment options, including the risks and benefits of antiviral therapy. Immunization against both hepatitis A and hepatitis B is recommended because people with chronic liver disease may be at increased risk for fulminant hepatitis A or B, and coinfection with hepatitis B is associated with a greater risk of disease progression and hepatocellular carcinoma.[31,32]

Table 3: Diagnostic tests to screen for coexisting liver disease

Coexisting liver disease	Diagnostic tests
Hepatitis B	HBsAg followed by HBeAg, anti-HBe and HBV DNA
Autoimmune hepatitis	ANA, SMA, IgG
Hemochromatosis	Ferritin, Fe-saturation, followed by genetic testing
Wilson's disease	Ceruloplasmin, 24-h urine copper
Alpha-1 antitrypsin deficiency	Alpha-1 antitrypsin serum level
Primary biliary cirrhosis	AMA, IgM

Note: HBsAg = hepatitis B surface antigen, HBeAg = hepatitis B e antigen, ANA = antinuclear antibodies, SMA = smooth muscle antibodies, IgG = immunoglobulin G, AMA = antimitochondrial antibodies, IgM = immunoglobulin M.

Table 2: Diagnostic evaluation of hepatitis C viral infection

	Screening test				
Step in diagnosis	Enzyme immunoassay	RIBA	Qualitative PCR*	Quantitative HCV RNA†	Genotyping
Screening for HCV antibodies	+	–	–	–	–
Confirmation of HCV antibodies	–	+	–	–	–
Confirmation of HCV infection	–	–	+	±	–
Evaluation of chances of treatment response	–	–	–	+	+
Evaluation of virological response during treatment	–	–	+	±	–
Evalualtion of virological response after treatment	–	–	+	–	–
Determination of treatment length	–	–	–	±	+

Note: RIBA = recombinant immunoblot assay, PCR = polymerase chain reaction, + = indicated, – = not indicated, ± = limited benefit or not recommended at present.
*Qualitative PCR with detection limit of 100 copies of HCV RNA/mL serum.
†Quantitative HCV RNA by PCR or branched-chain DNA.

Among the many factors that influence the decision to treat or not is the severity of the disease, likelihood of response to treatment, concomitant medical problems, age of the patient and contraindications for the use of interferon or ribavirin (Table 4). Treatment with interferon and ribavirin is recommended for patients with confirmed HCV infection who are expected to benefit from antiviral therapy after a complete clinical assessment and review of the contraindications has been completed. Combination treatment should be considered for patients with elevated liver function tests who have never been treated with interferon (interferon naïve) and for those who have relapsed after an initial response to monotherapy with interferon. Patients at greatest risk for disease progression (e.g., those with evidence of moderate inflammation or fibrosis on liver biopsy) should be given treatment priority. For patients with normal liver enzymes or for those in which aminotransferase levels failed to return to normal or HCV RNA failed to clear during monotherapy with interferon (nonresponders), treatment is currently not recommended outside clinical trials. Retreatment of nonresponders with interferon monotherapy results in response rates below 15%, and combination treatment with interferon alpha-2b and ribavirin for 6 months seems not to improve sustained response rates.[33–37]

Table 4: Indications and contraindications for treatment with alpha-2b interferon and ribavirin

Indications for combination treatment

- Confirmed HCV RNA positive by polymerase chain reaction
- Persistently elevated liver function tests (for more than 3 mo)
- Never treated with interferon or recurrence of HCV after initial response to interferon (i.e., relapse)
- Benefit of treatment anticipated in context of estimated life expectancy, given patient's age and comorbidities

Contraindications for combination treatment

- Decompensated liver disease
- Active alcohol use or intravenous drug use
- Pregnancy or noncompliance with contraception
- Noncompliance with treatment or monitoring of therapy
- Coexisting medical conditions including:
  - Anemia, neutropenia or thrombocytopenia
  - Significant ischemic heart disease
  - Congestive heart failure, arrhythmia
  - Cerebrovascular disease
  - Uncontrolled hypertension
  - Renal failure
  - Diabetes with retinopathy
  - Seizure disorder
  - Major uncontrolled psychiatric disease
  - Active autoimmune disease

Interferon treatment of patients with advanced cirrhosis can be associated with severe side effects and is contraindicated for patients with decompensated cirrhosis.[38,39] On the basis of the side effect profiles (Table 5), interferon and ribavirin are contraindicated if a patient has certain coexisting medical conditions. Because ribavirin can produce significant embryotoxic or teratogenic effects in several animal species and has a prolonged washout period from intracellular compartments,[40] strict compliance with contraceptive methods is required during and for 6 months after therapy for all patients.

Monotherapy with interferon alpha-2b or other interferons, should be reserved for patients who cannot tolerate ribavirin. Dosing schedules of interferons and long-acting pegylated interferons, alone and combined with ribavirin or other antiviral agents, are still being investigated; these

Table 5: Side effects of alpha-2b interferon and ribavirin

Agent; system affected	Side effect profile
Alpha-2b interferon	
Systemic	Fatigue, fever, anorexia, weight loss, myalgias, arthralgias, reversible hair loss
Hematologic	Leukopenia, thrombocytopenia, anemia
Neuropsychiatric	Anxiety, irritability, depression, suicidal ideation, sleep disturbance, drug craving, difficulty concentrating, cognitive changes, delirium, psychosis, paresthesias, hearing loss, tinnitus, visual loss, seizures, coma
Infectious	Increased susceptibility to bacterial infections, sepsis
Gastrointestinal	Nausea, vomiting, diarrhea, abdominal cramps
Autoimmune	Auto-antibodies (antinuclear, anti-thyroid, rheumatoid factor), hyper- and hypothyroidism, arthritis, vasculitis, psoriasis, erythema multiforme, diabetes mellitus, hepatitis
Other	Proteinuria, interstitial nephritis, nephrotic syndrome, cardiac arrhythmias, congestive heart failure, pneumonitis, graft rejection
Ribavirin	
Hematologic	Dose-dependent hemolytic anemia
Reproductive	Teratogenic effects
Other	Cough, dyspnea, pharyngitis, nausea, rash, pruritus, insomia

combinations should not be offered outside clinical trials or centres with special expertise.[41,42]

Patients with normal alanine aminotransferase levels

Approximately 25% of patients with chronic HCV infection have persistently normal alanine aminotransferase levels.[43,44] Liver biopsies indicate some degree of chronic hepatitis in the majority of these patients, but fibrosis or cirrhosis is less common.[30,45] Serfaty and colleagues[46] reported that monotherapy with interferon resulted in lower sustained response rates in patients with normal liver enzyme levels than in those with elevated levels. More importantly, treatment-induced elevations of liver enzymes have also been observed, and the underlying liver disease might be exacerbated if the relationship between viral replication and the host immune response is altered.[46,47] Treatment with interferon is therefore not recommended, and combination treatment with interferon and ribavirin has not been studied in these patients yet.[17] Asymptomatic patients without stigmata of chronic liver disease should be reviewed periodically because treatment strategies may change as more effective antiviral agents with fewer side effects become available in the future.

Interferon-naïve patients with elevated alanine aminotransferase levels

Until recently, monotherapy with 3 million IU interferon 3 times per week for 12 months was the accepted standard of treatment for patients with elevated liver enzymes and at least moderate neuroinflammatory activity or fibrosis on liver biopsy.[17] Normalization of aminotransferase levels and the disappearance of serum HCV RNA has been reported in about 40% of patients at the end of such treatment; however, a sustained virological response was achieved in only 15%–20% of patients.[8,9] There is accumulating evidence that the sustained virological response, when achieved, is durable and prevents the progression of disease.[48,49]

Combination antiviral treatment with interferon alpha-2b and ribavirin was evaluated recently in 2 large, randomized, placebo-controlled clinical trials.[15,16] Only patients with elevated liver enzymes over a 6-month period and with confirmed HCV infection by polymerase chain reaction and liver biopsy were included in the trials; those with significant coexisting medical conditions or decompensated cirrhosis were excluded from both studies. Most patients had HCV genotypes 1, 2 or 3, and a few patients had cirrhosis on the pretreatment liver biopsies. In the US multicentre trial 912 patients were randomized to receive interferon alpha-2b and ribavirin or interferon alpha-2b and placebo for 24 or 48 weeks.[16] In the international trial 832 patients were randomized as in the US trial, but there was no 24-week interferon–placebo group.[15] The dosage for interferon alpha-2b was 3 million IU subcutaneously 3 times per week; ribavirin was given orally and adjusted for the patient's weight (i.e., 1000 mg for patients < 75 kg and 1200 mg for those > 75 kg). Main outcome measures in the 2 studies were sustained virological response rates (i.e., undetectable serum HCV RNA 6 months after treatment) and histological improvement 24 weeks after treatment when compared with the pretreatment liver biopsy. Patients were stratified according to pretreatment variables known to influence interferon response (i.e., genotype, viral load and presence or absence of cirrhosis). The results of these trials expand on those of earlier smaller trials[50–52] and have changed our current treatment strategies.

Both studies reported that the rate of sustained virilogical response was higher for patients who received an interferon alpha-2b plus ribavirin combination for 48 weeks than for those who received interferon alone.[15,16] Reduced efficacy was associated with HCV genotype 1, a baseline viral load of $\geq 2 \times 10^6$ copies/mL, the presence of cirrhosis, age above 40 years and male sex.[15,16] Patients with HCV genotypes 2 and 3 showed a 64%–69% sustained response rate after 24 weeks of combination therapy, and extending therapy to 48 weeks did not increase response rates irrespective of the viral load.[15,16] However, patients with HCV genotype 1 and high viral titers or cirrhosis did achieve a higher sustained virological response rate with 48 weeks of treatment than with 24 weeks.[15,16] All groups showed histologic improvement; however, it was more common in the 48-week combination group than in the 24-week combination and interferon monotherapy groups. Although viral genotype 1 and high viral load are predictors of poorer response, patients should not be excluded from treatment because up to 28% of these patients may still obtain a sustained virological response.[15] Combination therapy was discontinued for adverse events in 8% and 19% of patients in the 24- and 48-week treatment groups, respectively.[15] Dose reduction or discontinuation for adverse effects was more common in patients receiving combination therapy. The most common reason for dose reduction was anemia[15,16] and for discontinuation, depression.[16] Hence, careful laboratory and clinical monitoring throughout the treatment period is required, and physicians should be familiar with indications, contraindications and side effects of combination antiviral therapy.

Patients previously treated with interferon monotherapy who relapsed

Roughly half of the patients who are treated successfully with interferon monotherapy will relapse after treatment is stopped.[8] Most of these patients will respond to a second course of interferon, but higher than standard doses of interferon and treatment periods longer than 1 year or treatment with consensus interferon is required to achieve a sustained response in 20%–50% of patients.[33,34,53] Combination treatment with interferon alpha-2b and ribavirin for 24 weeks has recently been shown to result in a sustained viro-

logical response in 49% of relapsers compared with only 5% of those treated with standard doses of interferon a second time;[54] sustained response rates varied between 100% (for patients with genotypes other than 1 and a baseline viral load $\leq 2 \times 10^6$ copies/mL) and 25% (for patients with genotype 1 and a baseline viral load $\geq 2 \times 10^6$ copies/mL). Hence, patients who have relapsed after interferon monotherapy should be offered combination treatment. Whether combination treatment beyond 6 months will increase sustained virological response rates in relapsed patients with unfavorable response factors remains to be determined.

Monitoring of therapy and follow-up

Close clinical and laboratory monitoring is required throughout the treatment period.[17] Most patients receiving interferon experience influenza-like symptoms, which diminish with continued treatment. Later side effects include bone marrow suppression, thyroid abnormalities and neuropsychiatric effects (Table 5).[8,55] Ribavirin predictably induces hemolytic anemia, which may be especially severe in patients with preexisting bone marrow suppression and can be life threatening for patients with significant cardiovascular or cerebrovascular disease. The hemoglobin usually falls in the first 2–4 weeks of treatment and then stabilizes in most patients. Complete blood counts with differential should be measured at least every 2 weeks in the first months of treatment and then monthly, and liver function tests should also be done monthly. Thyroid function tests and a urinanalysis should be done every 3 months. Following treatment a sensitive, qualitative polymerase chain reaction assay for HCV RNA should be performed, and liver enzymes should be assessed at 6 or 12 months.

Failure of serum alanine aminotransferase levels to return to normal or HCV RNA to clear by 3 months was a strong predictor of interferon monotherapy treatment failure.[56–58] However, some patients with cirrhosis or steatosis may continue to have abnormal liver enzyme levels despite a virological response. There is conflicting data from clinical trials that evaluated combination treatment with regard to the predictive value of early viral clearance. In one study[16] up to 14% of patients who were positive for HCV RNA by polymerase chain reaction at 3 months eventually became sustained responders; however, patients who failed to clear by 6 months did not achieve a sustained virological response.[16,54] Hence, treatment should be discontinued if there is no clearance of HCV RNA by polymerase chain reaction after 6 months.

There is currently no known effective treatment for those who do not respond to combination therapy. However, these patients should be followed clinically for the progression of liver disease and should be considered for new treatment protocols. Sustained virological responders are likely to maintain their improved histology and may be at reduced risk for hepatocellular carcinoma.[25,59,60] Nevertheless, a small fraction will relapse, and patients with cirrhosis, in particular, will still be at risk for hepatocellular carcinoma even after viral clearance. Therefore, all patients should continue to be followed, and screening for hepatocellular carcinoma should be offered to those with cirrhosis.[61]

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