

## Guidelines

### Management of Chronic Hepatitis C Infection

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#### Who Should Be Treated?

Patients with anti-HCV, HCV RNA, elevated serum aminotransferase levels, and evidence of chronic hepatitis on liver biopsy, and with no contraindications, should be offered therapy with the combination of alpha interferon and ribavirin. The National Institutes of Health Consensus Development Conference Panel recommended that therapy for hepatitis C be limited to those patients who have histological evidence of progressive disease. Thus, the panel recommended that all patients with fibrosis or moderate to severe degrees of inflammation and necrosis on liver biopsy should be treated and that patients with less severe histological disease be managed on an individual basis. Patient selection should not be based on the presence or absence of symptoms, the mode of acquisition, the genotype of HCV RNA, or serum HCV RNA levels.

Patients with cirrhosis found through liver biopsy can be offered therapy if they do not have signs of decompensation, such as ascites, persistent jaundice, wasting, variceal hemorrhage, or hepatic encephalopathy. However, interferon and combination therapy have not been shown to improve survival or the ultimate outcome in patients with preexisting cirrhosis.

Patients older than 60 years also should be managed on an individual basis, since the benefit of treatment in these patients has not been well documented and side effects appear to be worse in older patients. However, even patients in their late seventies have been successfully treated for hepatitis C.

The role of interferon therapy in children with hepatitis C remains uncertain. Ribavirin has yet to be evaluated adequately in children, and pediatric doses and safety have not been established. Thus, if children with hepatitis C are treated, monotherapy is recommended, and ribavirin should not be used outside of controlled clinical trials.

People with both HCV and HIV infection should be offered therapy for hepatitis C as long as there are no contraindications. Indeed, hepatitis C tends to be more rapidly progressive in patients with HIV co-infection, and end-stage liver disease has become an increasingly common cause of death in HIV-positive persons. For these reasons, therapy for hepatitis C

should be recommended even in HIV-infected patients with early and mild disease. Once HIV infection becomes advanced, complications of therapy are more difficult and response rates are less. The decision to treat people co-infected with HIV must take into consideration the concurrent medications and medical conditions. The efficacy of peginterferon and ribavirin in HIV-infected people has been tested in only a small number of patients. Ribavirin may still have significant interactions with other antiretroviral drugs.

In many of these indefinite situations, the indications for therapy should be reassessed at regular intervals. In view of the rapid developments in hepatitis C today, better therapies may become available within the next few years, at which point expanded indications for therapy would be appropriate.

Patients with acute hepatitis C are a major challenge to management and therapy. Because such a high proportion of patients with acute infection develop chronic hepatitis C, prevention of chronicity has become a focus of attention. In small studies, 83 to 100 percent of persons treated within 1 to 4 months of onset have had resolution of the infection. What is unclear is what dose, duration, and regimen of treatment to use. A practical regimen is peginterferon monotherapy for 24 weeks. The possible role for ribavirin, for short courses of therapy, and for lower doses of peginterferon are under evaluation.

In patients with clinically significant extrahepatic manifestations, such as cryoglobulinemia and glomerulonephritis, therapy with alpha interferon can result in remission of the clinical symptoms and signs. However, relapse after stopping therapy is common. In some patients, long-term or maintenance alpha interferon therapy can be used despite persistence of HCV RNA in serum if clinical symptoms and signs resolve on therapy.

#### Who Should Not Be Treated?

Therapy is inadvisable outside of controlled trials for patients who have:

- clinically decompensated cirrhosis because of hepatitis C

- normal aminotransferase levels
- a kidney, liver, heart, or other solid-organ transplant
- specific contraindications to either monotherapy or combination therapy.

Contraindications to alpha interferon therapy include severe depression or other neuropsychiatric syndromes, active substance or alcohol abuse, autoimmune disease (such as rheumatoid arthritis, lupus erythematosus, or psoriasis) that is not well controlled, bone marrow compromise, and inability to practice birth control. Contraindications to ribavirin and thus combination therapy include marked anemia, renal dysfunction, and coronary artery or cerebrovascular disease, and, again, inability to practice birth control.

Alpha interferon has multiple neuropsychiatric effects. Prolonged therapy can cause marked irritability, anxiety, personality changes, depression, and even suicide or acute psychosis. Patients particularly susceptible to these side effects are those with preexisting serious psychiatric conditions and patients with neurological disease.

Strict abstinence from alcohol is recommended during therapy with interferon. Interferon therapy can be associated with relapse in people with a previous history of drug or alcohol abuse. Therefore, alpha interferon should be given with caution to a patient who has only recently stopped alcohol or substance abuse. Typically a 6-month abstinence is recommended before starting therapy, but this should be applied only to patients with a history of alcohol abuse, not to social drinkers. Patients with continuing alcohol or substance abuse problems should only be treated in collaboration with alcohol or substance abuse specialists or counselors. Patients can be successfully treated while on methadone or in an active substance abuse program. Indeed, the rigor and regular monitoring that accompany methadone treatment provide a structured format for combination therapy. The dose of methadone may need to be modified during interferon-based therapy for hepatitis.

Alpha interferon therapy can induce autoantibodies, and a 24- to 48-week course triggers an autoimmune condition in about 2 percent of patients,

particularly if they have an underlying susceptibility to autoimmunity (high titers of antinuclear or antithyroid antibodies, for instance). Exacerbation of a known autoimmune disease (such as rheumatoid arthritis or psoriasis) occurs commonly during interferon therapy.

Alpha interferon has bone marrow suppressive effects. Therefore, patients with bone marrow compromise or cytopenias, such as low platelet count ( $< 75,000$  cells /  $\text{mm}^3$ ) or neutropenia ( $< 1,000$  cells /  $\text{mm}^3$ ) should be treated cautiously and with frequent monitoring of cell counts. These side effects appear to be more common with peginterferon than standard interferon.

Ribavirin causes red cell hemolysis to a variable degree in almost all patients. Therefore, patients with a preexisting hemolysis or anemia (hemoglobin  $< 11$  grams [g] or hematocrit  $< 33$  percent) should not receive ribavirin. Similarly, patients who have significant coronary or cerebral vascular disease should not receive ribavirin, as the anemia caused by treatment can trigger significant ischemia. fatal myocardial infarctions and strokes have been reported during combination therapy with alpha interferon and ribavirin.

Growth factors such as erythropoietin to raise red blood cell counts or granulocyte stimulating factor to raise neutrophil counts have been used successfully to treat patients with cytopenias during combination therapy. The proper role, dose, and side effects of these adjunctive therapies have yet to be defined.

Ribavirin is excreted largely by the kidneys. Patients with renal disease can develop hemolysis that is severe and even life-threatening. Patients who have elevations in serum creatinine above 2.0 mg per deciliter (dL) should not be treated with ribavirin.

Finally, ribavirin causes birth defects in animal studies and should not be used in women or men who are not practicing adequate means of birth control. Alpha interferon also should not be used in pregnant women, as it has direct antigrowth and anti-proliferative effects.

Combination therapy should therefore be used with caution. Patients should be fully informed of the potential side effects before starting therapy.