Patients with chronic hepatitis C – Who should not be treated?

Andreas Schüler MD, Michael Peter Manns MD

A Schüler, MP Manns. Patients with chronic hepatitis C – Who should not be treated? *Can J Gastroenterol* 2000; 14(Suppl B):63B-66B. The decision to treat a patient with chronic hepatitis C (CHC) is based on what is known about the risk factors for developing liver cirrhosis or hepatocellular carcinoma, as well as on conditions that contraindicate therapy or impair therapy effectiveness. Several factors, including age, treatment side effects, disease severity, concurrent diseases and life conditions, may render treatment decisions more difficult. This review focuses on identifying CHC patients who should not receive treatment.

Key Words: *Chronic hepatitis C; Human immunodeficiency virus; Interferon; Ribavirin*

Patients atteints d'une hépatite C chronique - Qui ne doit-on pas traiter ?

RÉSUMÉ : La décision de traiter un patient atteint d'une hépatite C chronique (HCC) se fonde sur ce que l'on connaît des facteurs de risque pour le développement d'une cirrhose du foie ou d'un carcinome hépatocellulaire, de même que sur les affections qui contre-indiquent un traitement ou compromettent l'efficacité du traitement. Plusieurs facteurs incluant l'âge, les effets secondaires du traitement, la sévérité de la maladie, les maladies concomitantes et le mode de vie, peuvent compliquer les décisions relatives au traitement. La présente revue de la littérature scientifique se concentre sur l'identification des patients atteints d'une hépatite C chronique et qui ne devraient pas recevoir de traitement.

Interferon (IFN) alpha is the standard treatment option for chronic hepatitis C (CHC) infection. Combination therapy with ribavirin enhances viral eradication and has become the treatment of choice (1-3). The decision to treat a patient with CHC is based on what is known about the risk factors for developing liver cirrhosis or hepatocellular carcinoma, as well as on conditions that contraindicate therapy or impair therapy effectiveness. Several factors, including age, treatment side effects, disease severity, concurrent diseases and life conditions, may render treatment decisions more difficult. These factors have been identified retrospec-

tively in various trials but have not been validated prospectively.

Metabolic factors, for example, severe hepatic iron overload induced by alcohol abuse or hemochromatosis, may deteriorate response to IFN, and iron depletion should be considered in those patients (4-7). Fatty liver disease (often found in patients with type II diabetes), hyperlipidemia, alcohol abuse or obesity, may also be regarded as barriers to treatment response. Reduction of obesity, strict treatment of diabetes and abstinence from alcohol consumption should precede IFN treatment.

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Department of Gastroenterology and Hepatology, Center of Internal Medicine, Hannover Medical School, Hannover, Germany
Correspondence and reprints: Dr Andreas Schüler, Department of Gastroenterology and Hepatology, Center of Internal Medicine, Hannover Medical School, Carl Neuberg Strasse 1, D-30625 Hannover, Germany. Telephone 49-511-532-3305, fax 49-511-532-4896, e-mail schueler.andreas@mh-hannover.de

HEPATITIS C VIRUS GENOTYPE

Most studies suggest that hepatitis C virus (HCV) infection with genotype 1 is more aggressive, responds less well to IFN, and recurs more rapidly after orthotopic liver transplantation than infection with genotypes 2 and 3. Patients with genotype 1b infection tend to be older and have transfusion-acquired infection rather than transmission via intravenous drug use.

Several large treatment studies have indicated that high viral load, HCV genotype 1b, long disease duration and transfusion-acquired infection render response to IFN therapy less likely (8-13). The response rate to IFN is inversely correlated to the HCV RNA concentration (14-17). Initial response rates of patients with genotype 1 range from 0% to 30%, to as high as 60% to 70% of those with genotypes 2 and 3 (8,14,16-20).

In contrast to relapsed patients, those unresponsive to IFN or patients who exhibited viral breakthrough during therapy are unlikely to respond to a second treatment course.

AGE

Those older than 60 years of age should only be treated on an individual basis because most of these patients have a combination of unfavourable factors, including long disease duration, transfusion-acquired disease, genotype 1b infection and advanced fibrosis. It is questionable whether even successful treatment will add to their life expectancy.

MILD DISEASE

According to the National Institutes of Health recommendations, patients with minimal inflammatory activity should not be treated because of their good long term prognosis. However, disease duration, an important factor for the response to IFN, will be prolonged. Therefore, treatment should be considered in young patients who have a short disease duration and low inflammatory activity. The majority of older patients with minimal hepatitis activity will not develop liver cirrhosis.

An alternative approach of waiting for better emerging therapies in patients with histologically mild hepatitis (with no more than grade 1 inflammatory activity or stage 1 fibrosis in the absence of clinical signs of advancing disease) is discussed insufficiently in the current literature.

CIRRHOSIS

Patients with cirrhosis are less likely to respond to IFN (21). The efficacy of IFN monotherapy (3 to 6 MU three times a week) for six to 12 months has been evaluated in four randomized controlled studies that allowed separate assessment of 212 patients with cirrhosis (22-25). Sustained biochemical response was observed in 9% to 16%. Early viral clearance, which predicts the probability of sustained response, was lower in cirrhotic patients, and the risk of viral breakthrough was higher.

However, like all predictive factors, cirrhosis alone is insufficient to exclude a patient from treatment. Thus, in as-

sessing cirrhotic patients, the possible effect of cirrhosis on treatment response should be considered in conjunction with age, viral load and genotype. Nevertheless, thrombocytopenia and leukopenia will render IFN treatment impossible because bone marrow suppression by IFN may enhance the risk of bleeding and may impair bacterial defence. The decision to treat in those cases should be individualized, taking into account age, general condition and the extent of portal hypertension. For cirrhotic patients, combination therapy with ribavirin and a lower IFN dose may be more favourable than IFN monotherapy.

Patients with decompensated liver cirrhosis are not candidates for IFN treatment but should be evaluated for liver transplantation.

CONCURRENT CONDITIONS

There are several diseases that may be aggravated by IFN therapy, for instance, autoimmune diseases (26,27). Common diseases – including autoimmune thyroid disease, chronic inflammatory bowel disease or autoimmune hepatitis – are contraindications for IFN therapy, even if they are in remission (28).

Patients with severe coronary heart disease should not be treated with ribavirin because hemolytic anemia may cause myocardial infarction.

Due to the neurotoxic effects of IFN, patients with psychiatric disorders or seizures should not receive IFN therapy (29,30). Seizures may occur even after a single IFN injection. Patients with a history of endogenous depression may develop suicidal tendencies and in general should not be treated with IFN; studies evaluating the safety of antidepressant use in IFN patients are lacking.

Older patients with poor nutrition are more prone to symptomatic side effects, which may limit treatment. Patients with a predisposition for bacterial infections will often develop an infection during IFN therapy. In patients with advanced cirrhosis, the risk of bacterial infection is high and can be life-threatening (31).

In many older patients, it is not only the existence of poor prognostic factors for antiviral treatment, but also concurrent diseases of the heart, kidney, lung and arterial vessels that render IFN therapy difficult (32).

IFN treatment requires regular medical supervision. Patients who are not compliant are at a higher risk of serious adverse events. Drug and alcohol abusers especially should not be treated as long as they are addicted. If side effects may mimic withdrawal symptoms and lead to premature cessation of therapy.

Concurrent infection with other hepatitis viruses hampers successful treatment of CHC. Patients with human immunodeficiency virus (HIV) infection will respond poorly to IFN therapy once the level of CD4 helper cells falls below 200 to 250/mL.

Treatment of HIV and HCV co-infection after AIDS develops is of no value. The effect of the new protease inhibitors on HIV has not been examined in such patients. The decision to treat HIV and HCV co-infection must be indi-

visualized. Modification of the course of HIV with protease inhibitors will have to be considered. IFN administration with other antiretrovirals, such as AZT, seems safe but cotreatment with protease inhibitors has not been examined.

Patients with inborn or acquired immunodeficiency states are less likely to respond to IFN. The same is true for patients who are treated with immunosuppressive drugs at high doses. In patients who have received an organ transplant, IFN may cause acute graft rejection.

NORMAL LIVER ENZYMES

Hepatitis C patients with persistently normal transaminase levels should not be treated with IFN because they seem to have a good long term prognosis in general, respond less well to IFN therapy and may exhibit transaminase flares during and after therapy (33-38). Usually fibrosis is absent or minimal, and cirrhosis rarely develops. Patients with persistently normal alanine aminotransferase levels have a slow rate of fibrosis progression; the expected median time to cirrhosis is 80 years (39).

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The long term outcome of anti-HCV-positive subjects with normal serum alanine aminotransferase is unknown. The discovery of a relatively long duration of HCV infection in many of these patients is consistent with a good prognosis.

Repeated measurement of liver enzymes is recommended for six months before therapy in order to rule out fluctuating transaminases at a low level.

CONCLUSIONS

Since the establishment of IFN therapy for CHC infection, much has been learned about viral and host factors that influence treatment outcome. This knowledge will help to identify patients who are more likely to benefit from IFN treatment and to recognize those with contraindications, in order to avoid severe side effects. It is important to consider not only negative therapeutic factors in absolute terms, but also each patient's individual health. IFN therapy is not clearly indicated in patients with a predictable and good long term prognosis or in those with poor response to IFN. In some patients, elimination of unfavourable metabolic factors should precede antiviral therapy.

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