

State-of-the-Art Interferon Therapy for Chronic Viral Hepatitis

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Presentation Summary

Interferon (IFN) therapy is frequently used to treat chronic viral hepatitis caused by the hepatitis B virus (HBV) or hepatitis C virus (HCV). The goals of treatment include viral clearance and reduction of damage to the liver to prevent or delay cirrhosis, liver cancer, the need for transplantation, and death. In patients infected with HCV—a far more common cause of chronic hepatitis than HBV—the best indicator of initial response to IFN is loss of HCV ribonucleic acid (RNA), as determined by reverse transcriptase

polymerase chain reaction. Extended treatment of HCV infection (longer than 6 months) at standard dosages (3 million international units three times a week) appears to be the most effective strategy for achieving a sustained response to IFN therapy.

In the treatment of HBV infection, the key patient selection criteria are a measurable HBV deoxyribonucleic acid (DNA) concentration, an elevated serum alanine aminotransferase (ALT) level, compensated liver disease, and human immunodeficiency virus negativity.

Hepatitis C Virus Infection: Natural History and Progression

The first randomized controlled trial of interferon (IFN) began in 1986, before the virus that causes hepatitis C had been identified. The results of that trial were published in 1989,¹ the same year that the hepatitis C virus (HCV) genome was cloned. Antibody testing methods were then introduced in 1990 at blood banks in the United States. In 1991, the Food and Drug Administration (FDA) approved the use of IFN alfa-2b (INTRON A) for the treatment of chronic HCV infection.

HCV infection, the most common cause of chronic liver disease, affects about 4 million individuals in the United States.² In this country, over 90% of cases of posttransfusion, non-A, non-B (NANB) hepatitis are caused by HCV.³ Histologic severity of disease is now graded as mild, moderate, or severe, depending on the degree of inflammation and presence of fibrosis. In the majority (70% to 80%) of HCV-infected people, the disease persists. Progressive disease leads to cirrhosis in about 20% of patients. Acute HCV infection develops into chronic disease in at least 80% of affected patients.¹ In

patients with chronic HCV infection, cirrhosis develops in 20% to 50% of patients within 10 to 20 years,⁴ with the subsequent risks of liver failure or hepatocellular carcinoma.³

Heavy alcohol consumption is an important cofactor in the development of cirrhosis.⁵ Other predisposing factors are older age, impaired immunity, the presence of viral coinfections, and possibly infection with HCV genotype 1.⁶⁻¹⁰

Biopsy

Liver biopsy constitutes the standard of practice for patients with chronic liver disease. The purpose of biopsy is to confirm the diagnosis, stage the disease, exclude other potential causes of liver disease, determine the prognosis, and justify treatment with IFN or other agents. If biopsy reveals cirrhosis, the physician needs to discuss treatment options with the patient. These include liver transplantation for those patients with evidence of decompensated liver disease, as well as screening for liver cancer.

Goals of IFN Therapy

The goal of IFN therapy is to suppress viral replication as well as to reduce the long-term necroinflammatory activity in the liver. Other goals of treatment include delaying or preventing the development of cirrhosis and minimizing the risk of systemic disease (eg, cryoglobulinemia). Through treatment, hopefully, hepatocellular carcinoma and the need for transplantation and deaths resulting from chronic viral hepatitis will be obviated.

The best measure of response to IFN is loss of HCV RNA as determined by reverse transcriptase polymerase chain reaction (RT-PCR). Initial trials in the United States and France have shown that IFN therapy will normalize alanine aminotransferase (ALT) values in about 50% of patients and also produce negative HCV RNA values in 40% of patients. Longer-term and higher-dose therapy

may result in initial viral clearance in up to 20% of patients, but less than 20% of patients have a sustained response beyond 1 to 2 years.

Prognostic Factors

The most important factor in a positive response to IFN therapy for HCV infection is a low pretreatment viral load.¹¹ Other factors associated with a positive response to therapy are mild histologic injury, normal hepatic iron concentrations, short duration of disease, young age, female sex, and a virus genotype other than type 1. These factors assist physicians in eliminating the likelihood of progression to cirrhosis, liver failure, and hepatocellular carcinoma (see Table 1).

Treatment of Chronic HCV Infection With IFN

Various studies have demonstrated that the best predictors of a sustained response to IFN are normalization of ALT values by week 12, and the loss of serum RNA by weeks 4 to 12, as determined by RT-PCR. Before initiating IFN therapy, Dr. Gish recommends measuring the patients' HCV RNA concentrations and counseling patients on their chances of achieving a sustained response. During treatment, Dr. Gish measures patients' HCV RNA concentrations by RT-PCR at 3 months to monitor response to IFN therapy. McHutchison et al¹³ determined that the best time to measure

Table 1. Rules of 20 for HCV Infection

- HCV infection clears spontaneously in less than 20% of patients
- IFN clears HCV infection in about 20% of patients
- Cirrhosis develops in 20% to 30% of patients with chronic HCV
- Cirrhosis takes about 20 years to develop in HCV-infected patients
- The risk of liver cancer in patients with HCV-related cirrhosis is 20% over the course of a decade

HCV RNA to predict either biochemical or virologic response is 12 weeks after the start of IFN therapy. Dr. Gish advises discontinuing IFN therapy if the level of serum HCV RNA has not changed at 3 months, but continuing treatment for at least 12 to 18 months if the level of serum HCV RNA is below the level of detection with RT-PCR.

About 50% of responders to conventional-dose IFN therapy (3 million international units three times weekly [3 MIU TIW] for 6 months) will experience a relapse, as indicated by the

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return of elevated ALT values and HCV RNA levels.^{12,13} In contrast, patients who have a sustained response to therapy usually remain free of HCV RNA for extended periods.¹⁴ Recent data indicate that longer courses of IFN are associated with a higher rate of sustained response. The following discussion of clinical study results focuses on the use of IFN alfa-2b, although IFN alfa-2a and consensus interferon are also approved for the treatment of chronic HCV infection (see *Current and Future Treatment Options*).

Poynard et al demonstrated the beneficial effects of extended IFN alfa-2b therapy in patients with chronic NANB hepatitis.¹⁵ In that trial, treatment with 3 MIU TIW for 18 months produced a better initial response and better sustained response than either 3 MIU TIW for 6 months, or 3 MIU TIW for 6 months followed by 1 MIU TIW for 12 months. In a multicenter trial¹⁶ of IFN therapy in 230 patients with chronic HCV infection, treatment for 2 years doubled (from 17% to 33%) the sustained response rate among the

patients who had experienced an initial response.

Shiffman et al¹⁷ administered IFN alfa-2b, 5 MIU TIW for 6 months, to 106 patients with chronic hepatitis C. The 47 responders were randomly assigned to either discontinue IFN therapy or follow a dose-tapering protocol over an additional 6 months. Ten of the 25 patients in the tapering group achieved a sustained biochemical response, compared with only two of the 21 patients who immediately stopped therapy. The difference was statistically significant ($P = 0.04$).

Although several studies have shown that IFN dose escalation produces a good initial response, the sustained response rate is similar to that seen with standard therapy. In a study by Lindsay et al in which response rates to IFN alfa-2b at dosages of 3, 5, or 10 MIU TIW were compared, higher doses failed to improve initial and sustained responses in patients who demonstrated complete or near-complete responses to IFN at week 12 of treatment. Patients with genotype 1a or hepatic fibrosis did tend to respond better to 5 MIU of IFN than to 3 MIU in this trial.¹⁸ However, dose escalation did not seem to improve the sustained response to therapy; moreover, high doses increase side effects, minimizing the usefulness of this approach.

Thus, longer duration of therapy at the standard dose of 3 MIU TIW appears to be a much better strategy than dose escalation to increase the sustained response rate.

Marcellin et al¹⁹ investigated patients' responses to retreatment with IFN alfa-2b. Of the 40 subjects they studied, 20 had demonstrated no response to initial IFN alfa-2b therapy (3 or 5 MIU TIW for 4 or 6 months), and 20 relapsed after having shown a complete response (normalization of ALT levels). Of the initial nonresponders, 15% responded to retreatment with the same regimen but then relapsed. In contrast, 90% of the initial responders responded to retreatment, and

one third of these new responses were sustained. Therefore, although retreatment of nonresponders has not been shown to induce a long-term response, retreatment of patients who initially responded and then relapsed after one course of IFN alfa-2b may result in a sustained response.¹⁹ Subsequent treatment strategies, such as daily therapy or combination therapy, need to be developed for patients who do not respond to IFN. These patients include the chronically immunosuppressed, especially patients who have undergone renal, heart, or liver transplantation; patients in chronic renal failure; decompensated cirrhotics (patients who need a liver transplant); patients coinfecting with human immunodeficiency virus (HIV); young children; and patients with multiple medical problems, for whom IFN therapy may be dangerous.

Current and Future Treatment Options

As of June 1998, the Food and Drug Administration (FDA) had approved three interferon formulations: alfa-2b, alfa-2a, and consensus. In addition, the combination of interferon alfa-2b and ribavirin has been approved for patients who relapse after therapy and will most likely be approved later in 1998 for use in patients naive to therapy.

Other current and future options in the treatment of HCV infection are shown in Table 2.

Hepatitis B Virus Infection Goals of IFN therapy

Hepatitis B virus (HBV) infection causes chronic disease in only about 5% of acutely infected adults.²⁰ IFN alfa-2b therapy is the standard of care, and the goals of treatment are similar to those for HCV infection. Data accumulated from clinical trials of IFN alfa-2b indicate that the following clinical outcomes can be expected: a 40% chance of clearance

of HBV DNA or hepatitis B e antigen (HBeAg); a 25% to 35% chance of HBeAg clearance in patients with long-term (about 3 to 5 years) normalization of ALT values; and prevention of, or a delay in, the development of cirrhosis. In addition, long-term studies suggest that IFN alfa-2b therapy decreases the rate of liver failure and transplantation.

Recent studies indicate that daily oral use of lamivudine is associated with response rates that are slightly better than historical results with IFN alfa-2b, but comparative studies must be done.

Prognostic Factors

A response to IFN alfa-2b is more likely in patients who have low pretreatment HBV DNA values, high pretreatment serum ALT values, histologic evidence of active disease, disease onset in adulthood, or a short duration of disease, and in those who test negative for HIV antibodies.

Table 2. Current and Future Options for Treating HCV Infection

Method	Comments
IFN alfa-2b (18 to 24 months) or IFN alfa-2a (12 months)	Standard of care
Daily IFN therapy	In clinical trials
IFN alfa-2b dose escalation	Rarely used
Phlebotomy	Research protocol
IFN alfa-2b dose tapering	Rarely used
Other IFNs	Prospective studies needed
IFN + ribavirin	Approved for patients who relapse after IFN; soon to be approved for IFN-naive patients
Thymosin alpha-1	Research in progress
Tucarecol	Research in progress
Herbal and nonprescription products	Not recommended

Treatment of Chronic HBV Infection With IFN Alfa-2b

Drs. Gish and Balart use the following criteria in selecting hepatitis B patients for IFN alfa-2b therapy:

- Measurable HBV DNA concentration (preferably < 200 pg/mL)
- Elevated ALT concentration (preferably > 200 IU/dL)
- Compensated liver disease
- HIV negativity

They consider liver biopsy essential in evaluating patients with HBV infection, because histopathologic findings help define long-term outcome.

Dr. Balart pointed out that immunosuppressive prednisone therapy for patients with very low ALT concentrations (<10 IU/dL) may be a good pretreatment strategy.²¹

The treatment of patients with chronic HBV infection and normal ALT levels is controversial because most of these patients do not respond to IFN therapy.

Dr. Gish does not treat silent carriers (people who are infected with HBV but have normal serum ALT levels), but he does check their ALT concentrations every 6 to 12 months. If the ALT level rises, Dr. Gish reassesses the patient's HBV DNA status. If viremia exists, he performs a liver biopsy because cancer can develop even in silent carriers.

Nucleoside Analogues

Nucleoside analogues such as lamivudine are a promising adjunct or alternative to IFN alfa-2b therapy. In patients with progressive liver disease who do not respond to IFN alfa-2b (eg, immunosuppressed patients, patients with high viral titers), these agents may be used to try to reduce the HBV DNA concentration before IFN alfa-2b therapy is reinstated. In a randomized, double-blind, dose-ranging trial of lamivudine²² in which 32 patients with chronic HBV infection were enrolled, lamivudine suppressed HBV

DNA to undetectable levels in all 22 of the patients who received either 100 mg or 300 mg daily for 12 weeks. The drug was active in IFN alfa-2b nonresponders and in subgroups that rarely respond to IFN alfa-2b. However, HBV DNA suppression was sustained in only six (19%) of the 32 patients, five of whom had not responded to IFN alfa-2b.

Treatment of Chronic Viral Hepatitis and Managed Care

Clinicians who treat chronic viral hepatitis in managed care settings must explain associated costs and outcomes to the insurance providers. Also, clinicians need to keep managed care health professionals, including therapeutics committee members and medical directors, informed about new data related to the diagnosis and treatment of HCV and HBV infections. Maintaining a computer database of pertinent references and citing them appropriately in consultation notes and correspondence is very helpful in communicating with other physicians and insurance companies and in justifying clinical decisions.

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