Initial results with recombinant interferon alfa-2b in patients with chronic hepatitis C: the United States experience

G L Davis

Abstract

Early experience with recombinant interferon alfa-2b in chronic hepatitis C (HCV) has shown that normalisation of serum alanine aminotransferase activities and reduction in hepatic inflammation can be achieved in about 40% of patients. This occurs with loss of viral replication as measured by polymerase chain reaction for HCV-RNA. Further studies are needed to identify patients most likely to respond to treatment and to investigate the issues of non-response and relapse when treatment is stopped. Alternative interferon treatment regimens, as well as other drugs and combinations of agents, need to be investigated.

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The purpose of this paper is to review the early experience with recombinant interferon in the treatment of HCV so that this may serve as a reference for comparison with other studies and a framework for the design of future clinical research in this area. The review will emphasise not only what has been established by these trials, but also what remains to be determined; namely, the several outstanding issues regarding interferon treatment of HCV.

Pilot studies

In the 1980s, there were several case reports describing the treatment of chronic non-A, non-B hepatitis with interferon (IFN).^{1,2} It was not until 1986, however, that the first systematic study of this form of treatment in well-characterised patients with chronic non-A, non-B hepatitis was reported by Hoofnagle and associates at the National Institutes of Health Liver Unit.³ In that study, 10 patients were treated with recombinant interferon alfa-2b at an initial dose of 5 million units (MU) daily (in most patients), with the dose decreased, as tolerated, to the lowest dose which would maintain a normal serum alanine aminotransferase activity. Serum alanine aminotransferase fell quickly to normal in six of 10 patients (complete response) and the rapidity of the alanine aminotransferase decrease suggested a direct antiviral effect. Surprisingly, this initial response was maintained after treatment was stopped in five of six patients who responded.

US studies

The encouraging results in the National Institutes of Health pilot study led to the implementation of several randomised controlled trials, including a placebo controlled study which was conducted by Di Bisceglie and colleagues, also at the National Institutes of Health.⁴ This trial compared a dose of 2 MU interferon alfa-2b, given subcutaneously three times per week for six months, with placebo given in the same schedule. Interestingly, although more than 60% of patients treated with IFN normalised their serum alanine aminotransferase at some point during the treatment period, breakthrough of serum alanine aminotransferase to abnormal values was common and such that only 33% maintained a normal alanine aminotransferase value at the end of treatment. In addition, most patients responding to treatment relapsed after treatment was stopped. This suggested that higher doses or treatment of a longer duration, similar to that used in the pilot study, might be more efficacious.

The United States multicentre study (Hepatitis Interventional Therapy group study) later confirmed the dose response effect of IFN treatment.⁵ In this large study, the probability of complete response was 38% in patients treated with a dose of 3 MU interferon alfa-2b three times weekly, but only 16% in those treated with 1 MU, and 4% in untreated controls (Fig 1). Histological improvement was seen in the 3 MU group and was characterised by reduction of lobular inflammation and a trend towards improvement of periportal inflammation (Fig 2). Interestingly, compared with Di Bisceglie's report, breakthrough in serum alanine aminotransferase was not seen. This study formed the basis for the licensing of interferon alfa-2b for the treatment of HCV (INTRON A; Schering-Plough) in the United States.

Comparison with European studies

Two European studies using an almost identical study design to the United States study subsequently reported a very similar complete response rate (normal alanine aminotransferase), and also showed a similar proportion of patients with histological improvement.^{6,7} These, and similar studies,⁸ formed an important foundation for the treatment of patients with HCV, but several questions still remain for improving our clinical treatment for these patients. How are patients

Section of
Hepatobiliary
Diseases,
University of Florida
College of Medicine,
Gainesville,
Florida, USA
G L Davis

Correspondence to:
Dr G L Davis,
Box J-214,
JHMHC,
University of Florida,
Gainesville,
Florida 32610-0214, USA.

Figure 1 Response rates for treated (1 and 3 MU IFN) and untreated patients.

* $p < 0.01$ † $p < 0.10$

Figure 2 Liver biopsy results after treatment with 3 MU IFN α -2b three times weekly for 24 weeks.

most appropriately selected for treatment? Are other dose regimens more effective? How should relapse be treated? Are other forms of treatment likely to be effective?

Patient selection

The appropriate selection of patients is based on the probability of altering the natural history of the disease, alleviating symptoms, and providing a cost effective treatment.⁹ These issues are not independent. Cost effectiveness assessments obviously require reasonable estimations of the natural history of disease in the disease group as a whole or, perhaps ideally, in individual patients. Unfortunately, this is not possible with any documented degree of accuracy in patients with chronic HCV. This dilemma is most evident in patients with chronic persistent hepatitis. It is assumed that these patients with mild histological severity will have a more slowly progressive

disease which will be far less likely to result in cirrhosis or hepatic failure. If this was true, treatment would be difficult to justify unless it was almost uniformly effective, without risk or side effects, and available at low cost. Few treatments, and certainly not IFN, meet all of these requirements. Recent reports now suggest, however, that chronic persistent hepatitis may cause progressive hepatic injury in many patients,^{10 11} and treatment may need to be considered despite a more insidious course. The natural history of disease in patients with more severe histological inflammation and injury (for example chronic active hepatitis, bridging necrosis, or fibrosis) is more likely to be progressive, and treatment can be undertaken more confidently.

Not only do we need to know whether the natural history of the disease demands treatment, we also need to know that intervention alters the natural course of disease. Data currently available are limited to short courses of treatment and, because relapse occurs in most patients after treatment has stopped, these short courses are unlikely to have any effect on the long term course of disease. Preliminary data documenting a reduction in hepatic inflammation,⁵⁻⁷ normalisation of raised procollagen values,¹² and a reduction in cytotoxic cytokines such as $TGF\beta$ ¹² in patients responding to treatment, however, implies that the disease course may be favourably affected by long term maintenance treatment or regimens that will prevent relapse. Obviously, a goal of future research studying the long term effect of treatment should be to document any improved hepatic function, delay in histological progression, and improved survival.

Cost effective intervention

Cost effectiveness can be improved in two ways; either by better patient selection or by improved treatment response. We should strive to achieve both. Patient characteristics before treatment have been analysed by ourselves and others to identify clinical predictors of response to IFN treatment. Although a number of differences between responders and non-responders have been identified with univariate testing,^{13 14} histological examination is the best predictor of response in a multivariate model.¹⁵ In our experience, 62% of patients with chronic persistent hepatitis achieve a complete response, while response occurs in only 35% of patients with chronic active hepatitis or cirrhosis. As discussed above, however, the natural history of chronic persistent hepatitis may not be sufficiently progressive or rapid to justify early treatment of these patients. This is an issue that deserves critical attention in future studies. The second issue is that of improved response. Preliminary data from studies evaluating higher doses of interferon, longer duration of treatment, and escalation of dose in non-responders have not shown any significant increase in response by doses above the currently recommended dose of 3 MU three times weekly for 24 weeks.¹⁶ It is possible

that, however, in the future, subgroups of patients will be identified who require higher or lower doses to achieve response.

Goals of treatment

Interferon is an antiviral agent which suppresses HCV replication below detectable values in patients responding to treatment.¹⁷ Relapse occurs in 50–80% of patients, however, after treatment has stopped.^{5–8} Thus, eradication of HCV is an uncommon event and, with the treatment regimens in current use, is not an appropriate goal of treatment. Treatment for patients who have relapsed has been shown to be effective in inducing response again;⁵ however, the most appropriate method of a further course of treatment has not been studied. The two logical alternatives for further treatment are to repeat the six month course which was successful originally, or to start long term treatment at the lowest dose which will maintain response. There are few or no data to support either of these alternatives at the present time. It is important, if long term treatment is considered, that we have a marker for the endpoint of treatment. These markers are likely to be virological but have not yet been identified.

Summary and conclusions

In summary, studies to date have shown clearly that recombinant interferon alfa-2b treatment of chronic HCV is effective. Normalisation of serum alanine aminotransferase and reduction of hepatic inflammation can be achieved in approximately 40% of patients.^{5–8} This is associated with loss of HCV replication, as measured by the polymerase chain reaction for HCV-RNA in liver and serum.¹⁸

Several outstanding issues remain despite these achievements. The natural history of the disease needs clarification so that appropriate patients can be selected for treatment. Fewer than 50% of patients respond to current regimens, so patients most likely to respond to IFN and those most in need of treatment to alleviate the course of their disease must be identified and offered treatment. Other interferon regimens, different drugs, and combinations of drugs need to be tested as alternate regimens for patients not responding to treatment or those predicted to have poor

response. Finally, markers of successful and permanent treatment response need to be identified.

There have been many major basic and clinical accomplishments in the field of HCV research over the last few years. There is still much more to be achieved.

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