Maintenance Interferon for Chronic Hepatitis C: More Issues Than Answers?

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In this issue of HEPATOLOGY, Ikeda et al.[1] describe use of long-term maintenance therapy with beta-interferon to prevent recurrent hepatocellular carcinoma (HCC) after surgical resection or alcohol ablation of primary HCC in patients with chronic hepatitis C virus (HCV). Twenty patients, 10 per group, were randomly assigned to either beta-interferon or no treatment after potentially curative surgery (n = 16) or alcohol ablation (n = 4). The two groups were well matched in terms of demographics, hepatitis serology, HCV-RNA positivity, and percent cirrhosis (85% overall). Although most were cirrhotic and some had significantly reduced serum albumin and platelet count, none had evidence of clinical decompensation. Nearly all HCCs were solitary (90% for both groups), all were less than 5 cm, 50% were less than 2 cm, none exhibited vascular invasion, and histology was moderately well differentiated. In general, treatment was well-tolerated, with few patients requiring dose reductions. However, one patient was discontinued from treatment for spontaneous retinal hemorrhage after 19 months of interferon. During follow-up, no patient in either group experienced clinical decompensation as manifest by ascites, encephalopathy, variceal hemorrhage, or spontaneous bacterial peritonitis.

Although the number of patients in this trial is too small to draw definitive conclusions, the preliminary data are striking: only 1 of 10 interferon-treated patients developed detectable recurrence of hepatoma, whereas 7 of 10 untreated patients had detectable recurrence ($P < .0004$). The implication of this result is that maintenance interferon might be considered for patients undergoing curative treatment for HCC.

The difference in outcome for interferon-treated and control patients followed for a relatively short period of time (median of 25 months) is so dramatic as to raise skepticism. Were the two groups truly matched at entry into the trial? Could the apparent beneficial effect of interferon simply reflect randomization of patients with a higher tumor burden or metastatic disease to the control arm? This kind of problem is inherent in small-scale trials.[2] Why was the tumor recurrence rate so high in the untreated group (70% of patients with recurrent HCC within 2 years of follow-up)? The HCCs were small, solitary, lacked vascular invasion, and were moderately well differentiated, consistent with a favorable prognosis. The high recurrence in the untreated arm again suggests an unrecognized bias in the randomization process. What is the evidence that interferon, particularly beta-interferon, is truly chemotherapeutic in HCC? The investigators cite studies suggesting that alfa-interferon is antiproliferative.[3,4] However, the clinical evidence suggests only modest or no efficacy of alfa-interferon in causing regression or controlling growth of HCC. Furthermore, to my knowledge there are no studies that have directly evaluated the antiproliferative or antineoplastic effects of beta-interferon in similar experimental models. Given the concerns regarding efficacy and the considerable potential for significant adverse effects of interferon therapy, one cannot currently recommend routine use of beta-interferon in prevention of HCC recurrence without confirmation of these initial observations in large, randomized, controlled trials.

Although the study focused on the use of interferon in the prevention of HCC recurrence, a broader question arises: What is the role of long-term interferon in preventing clinical complications of cirrhosis caused by chronic hepatitis C? Sixty to 70% of patients treated with current antiviral regimens fail to respond and remain infected with hepatitis C. Mounting evidence indicates that these virologic nonresponders experience reduction in hepatic inflammation and inhibition of hepatic fibrosis.[5-13] However, it is not known whether current antiviral regimens halt disease progression, prevent complications of cirrhosis, and reduce the risk of HCC. Progression of liver disease in patients with hepatitis C is linked to progressive fibrosis arising from ongoing hepatic inflammation,[14-15] and HCC develops mainly in patients with underlying cirrhosis.[16] Interaction between virus and host results in immune-mediated inflammation, which may be suppressed by specific interferons, interleukins, or related cytokines. For this reason, long-term maintenance therapy with interferon has been suggested as possible therapy to prevent disease progression and reduce risk of HCC. The recent decision by the National Institutes of Health (NIH) to conduct a multicenter treatment trial of virologic nonresponders with advanced stages of chronic hepatitis C (HALT-C Trial, Hepatitis C Antiviral Long-Term Treatment against Cirrhosis Trial) highlights the importance of this clinical and therapeutic issue.[17]

One study of virologic nonresponders showed a reduction in fibrosis with long-term interferon maintenance therapy compared with no treatment.[18] Liver biopsy was performed before and after a 6-month course of interferon. Patients who had histologic improvement on the biopsy done at 6 months

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NIH, National Institutes of Health; HALT-C, Hepatitis C Antiviral Long-Term Treatment against Cirrhosis Trial.

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(n = 53) were randomly assigned to either remain on interferon-alfa-2b treatment (n = 27), at a dose of 3 MU three times a week, or discontinue treatment (n = 26) and be followed prospectively for a total of 2.5 years. Maintenance interferon was associated with diminished hepatic inflammation and reduction in hepatic fibrosis (mean fibrosis score decreased from 2.5 to 1.7, and 80% of patients had sustained histologic improvement, $P < .03$). Untreated controls experienced ongoing hepatic inflammation and an increase in hepatic fibrosis over the same period of observation (mean fibrosis score increased from 2.2 to 2.4, with worsening of histology in 30%, $P < .01$). These observations suggested that long-term treatment with interferon could control hepatic inflammation and potentially halt or reduce hepatic fibrosis in the absence of viral clearance.

Another provocative study suggested that treatment of cirrhotic patients with interferon reduced the incidence of HCC.[19] Thirty-eight percent of untreated patients developed HCC with a mean of 4.4 years of follow-up compared with only 4% incidence in treated patients. These results are somewhat surprising, because treated patients received only a limited, 6-month course of interferon therapy. The beneficial effect on incidence of HCC was not limited to sustained responders but occurred also in nonresponders, those who had not achieved biochemical or virologic response. Three studies, encompassing 272 untreated patients, 371 nonresponders, and 60 sustained responders after interferon treatment, examined the impact of interferon therapy on occurrence of HCC in cirrhotic patients with hepatitis C.[16,20-22] The frequencies of HCC in these 3 groups were 15%, 4%, and 0%, respectively, suggesting a beneficial effect of interferon in prevention of HCC.

The above data strongly suggest a role for maintenance interferon in patients with advanced hepatitis C, to prevent both disease progression and development of HCC. However, multivariate analyses have suggested that clinical differences at the time of entry, not interferon therapy, correlated with the incidence of HCC.[16] Progression from cirrhosis to HCC was associated with genotype 1b, male gender, and age over 60, suggesting that host variables and viral characteristics may be more important in the development of HCC than antiviral therapy. A similar conclusion was reached in an independent retrospective analysis of the incidence of HCC among 163 cirrhotic patients with hepatitis C.[23] These analyses imply that the apparent reduction of HCC in interferon-treated patients may not be due to the antiproliferative or antineoplastic effects of interferon but rather to a bias that favors treatment for patients with less advanced disease.

Concerns about the quality of the published data notwithstanding, maintenance treatment may be effective. Certainly it is plausible that reduction of liver inflammation by interferon could slow the progression of fibrosis to cirrhosis, reduce the rate of new fibrosis in cirrhosis, reduce the likelihood of clinical decompensation, and delay the development of HCC. So, why not treat all patients with chronic hepatitis C based on current results? First, no study has conclusively shown that interferon slows disease progression, decreases clinical complications of decompensation of liver disease, reduces the need for transplantation, or lowers the risk of HCC. Second, interferon therapy at the rate of $800 per month is costly; the combination of interferon and ribavirin costs $1,200 to $1,500 per month. Third, both interferon and ribavirin carry significant risk of adverse reactions. Again, large trials are needed to assess risk-benefit and cost-effectiveness.

Which drug is optimal for maintenance therapy? Ribavirin would not be considered by most investigators for chronic administration because of its toxicity, mutagenicity, and lack of efficacy as monotherapy. While any of the currently available preparations of interferon could be used for maintenance, pegylated interferons may soon be approved and offer two advantages over standard formulations: ease of use (once weekly injection rather than 3 times weekly), and increased efficacy. Weekly injection will result in improved compliance in long-term maintenance protocols. With regard to efficacy, trials of pegylated interferons given by subcutaneous injection once a week have shown biochemical and virologic responses better than those achieved with standard formulations given 3 times a week.[24] Finally, the side-effect profile of pegylated interferons seems to be similar to that of standard formulations. These considerations have led to the use of pegylated interferon in the NIH-sponsored HALT-C trial.

In summary, the study by Ikeda et al.[1] is intriguing, adding to the literature that suggests that maintenance interferon therapy may slow disease progression and reduce rates of development of HCC. Proof, however, will require performance of large, randomized, controlled trials, such as the HALT-C trial that is now underway.

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