

Medical Writers' Circle

a series of articles

written by medical
professionals about
the management
and treatment of
Hepatitis C

Joanne C. Imperial, MD

Associate Professor of
Medicine, Stanford University
School of Medicine

The Role Of Antiviral Therapy In The Natural History Of Hepatitis C Fibrosis

The development of liver fibrosis is a critical event in the natural history of chronic hepatitis C virus infection. Fibrosis is the predominant cause of morbidity and mortality from this disease and is responsible for the development of liver decompensation, hepatocellular carcinoma and death in a percentage of chronically-infected individuals.

Liver biopsy is considered mandatory for accurate staging of early fibrosis. A recent prospective study was done to assess the accuracy of a combination of serum biochemical markers for diagnosing fibrosis, including early stages. Eleven serum markers were assessed, as well as the METAVIR fibrosis stage. A fibrosis score combining the most informative markers and taking into account age and gender was constructed. High negative-

predictive values were obtained for scores ranging from 0 to .10 and high positive-predictive values were obtained for scores ranging from .6 to 1.0. Using a combination of simple serum markers to predict fibrosis could potentially lead to a 50% reduction in the number of liver biopsies performed in patients with chronic HCV. A serum hyaluronic acid level of <110 mcg/l was associated with a 97% negative predictive value for significant fibrosis.

The effect on hepatic fibrosis using pegylated interferons has recently been studied by several investigators. Heathcote randomized 271 patients with bridging fibrosis or cirrhosis to receive either interferon alfa-2a 3MU TIW, peginterferon alfa-2a 90 mcg QW or peginterferon alfa-2a 180 mcg QW. SVR was reported in 8%, 15% and 30% of these treatment groups. In a subset of patients

who underwent paired liver biopsies, histologic response (greater than a 2-point decrease in a total Histologic Activity Index score) at week 72 was 31%, 44% and 51% respectively. Even among those individuals that did not have a sustained response to treatment, histologic improvement was observed in approximately 33% of patients. Poynard pooled individual data from 3010 treatment-naïve patients with pre- and post-treatment liver biopsies from four randomized treatment trials. Ten different regimens combining standard interferon, pegylated interferon, and ribavirin were compared. Improvement in inflammation and necrosis varied from 39% in patients treated with standard interferon monotherapy for 24 weeks to 73% in those treated optimally with peginterferon and ribavirin. All regimens reduced the annual rate of

Although the goal of antiviral therapy is to achieve sustained viral eradication, recent studies have suggested that secondary goals of preventing progression of fibrosis or liver cancer can be accomplished, even in treatment nonresponders. ■ ■ ■

fibrosis progression compared with pretreatment rates. Fibrosis stage, sustained viral response, age less than 40 years, body mass index of <27 kg/m, minimal pretreatment inflammation, and viral load less than 3.5 million copies/mL were independent factors associated with the absence of significant fibrosis after treatment in this analysis.

Although the goal of antiviral therapy is to achieve sustained viral eradication, recent studies have suggested that secondary goals of preventing progression of fibrosis or liver cancer can be accomplished, even in treatment nonresponders. Several retrospective studies to date and one recent prospective study have documented prevention of HCC after 24 or 48 weeks of therapy with interferon monotherapy in patients who do not have a sustained viral response. There is only one published, controlled trial to date using interferon maintenance therapy and the results demonstrated that continuing interferon for two years in a subpopulation of nonresponders stabilized fibrosis and reduced inflammation on serial liver biopsies.

Risk factors for progressive fibrosis include age >40 years at acquisition of HCV infection, presence of bridging fibrosis on initial liver biopsy, increased body weight with hepatic steatosis, excess alcohol consumption >25 g/d,

excess hepatic iron, and immunosuppression. There are no prospective studies that have looked at concomitant therapy using antifibrotic agents or cytoprotective drugs in prevention of hepatitis C fibrosis progression. Colchicine and ursodeoxycholic therapy have no direct antiviral effect, but no data is available regarding the role of these drugs as long-term therapy in patients with HCV cirrhosis. Vitamin E has some benefit in reducing ALT levels in patients with HCV infection, but has not been studied prospectively as an antifibrotic agent.

Ongoing studies are planned specifically to examine the role of antiviral therapy on progression of fibrosis and clinical hepatitis C-related liver disease. There are two studies that have been launched to evaluate maintenance therapy using pegylated interferons: the HALT-C trial, sponsored by the NIH, and the COPILOT (Colchicine vs PegIntron Long-Term), sponsored by Schering Hepatitis Innovations. Both studies are planning to evaluate the effect of four years of treatment on the progression of fibrosis and development of liver failure and/or hepatocellular carcinoma. Together, these studies should resolve the very important question regarding the role of antiviral therapy in the natural history of hepatitis C fibrosis. ■ ■ ■

References

1. Friedman SL. Evaluation of fibrosis and hepatitis C. *Am J Med* 107:27S-30S, 1999.
2. Heathcote EJ, Shiffman ML, Cooksley, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 343:1673-1680, 2001.
3. Poynard T, McHutchison J, Davis GL, et al. Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. *Hepatology* 32:1131-1137, 2000.
4. Poynard T, Ratziu V, Benhamou Y, Di Martino VD, Bedossa P, Opolon P. Fibrosis in patients with chronic hepatitis C: detection and significance. *Semin Liver Dis* 20:47-55, 2000.
5. Shiffman ML, Hofmann CM, Contos MJ, et al. A randomized, controlled trial of maintenance interferon therapy for patients with chronic hepatitis C virus and persistent viremia. *Gastroenterology* 117: 1165-1172, 1999.