

Medical Writers' Circle

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a series of articles
written by medical
professionals about
the management
and treatment of
hepatitis C

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Treatment of Chronic Hepatitis C: Impact on Natural History

Chronic hepatitis C affects 170 million individuals worldwide, with at least 4 million persons in the United States having been infected (1,2). In the United States, chronic hepatitis C virus (HCV) infection is now the leading cause of death from liver disease secondary to cirrhosis with liver failure and/or hepatocellular carcinoma (HCC) (1). Natural history studies indicate that 5% to 20% of patients with chronic hepatitis C will develop cirrhosis over a period of 20 to 25 years from the onset of infection (2). Progressive hepatic fibrosis is the main determinant of subsequent complications of portal hypertension such as ascites, variceal bleeding and hepatic encephalopathy that may eventuate in irreversible liver failure and death. In addition, advanced hepatic fibrosis is associated with a significant risk of HCC, and patients rarely develop HCC in the absence of cirrhosis (3). Once cirrhosis is present, the annual incidence rate of HCC ranges from 3% to 8%.

Since the original licensure of interferon alfa-2b in 1992, there have been substantial

advances in antiviral therapy related initially to the addition of ribavirin to standard interferon therapy in 1998 and in the recent few years to the use of peginterferon plus ribavirin (4). The sustained virological response (SVR) rate is now approximately 55% to 60% overall with current therapy, with 42% to 46% of patients with genotype 1 and 76% to 82% of patients with genotypes 2 or 3 having a SVR in the two registration trials of peginterferon alfa-2a and peginterferon alfa-2b plus ribavirin. As part of drug development, short-term goals of virological, biochemical and histological responses 6 months after completion of

therapy are regularly assessed and have been shown to be achievable in more than half of treated patients (Table 1). As a result of these incremental improvements in therapy, more than 500,000 Americans have received antiviral therapy (personal communication, Roche and Schering). This more widespread use of antiviral therapy for chronic hepatitis C begs the question of whether or not antiviral therapy affects the long-term natural history of chronic HCV infection. Preliminary data indicate that this is indeed the case, i.e., SVR persists long-term, fibrosis and inflammation are improved, the incidence of HCC is reduced,

TABLE 1

Short-term and Long-term Outcomes of Antiviral Therapy

Short-term (6 months after completion of therapy)

Improvement well established in patients with SVR in:

- Virological response
- Biochemical response
- Histological response

Long-term (greater than 6 months in those with an SVR)

Favorable outcomes recently documented in:

- Virological (and biochemical) responses
- Fibrosis scores
- Incidence of hepatocellular carcinoma
- Life expectancy

and life expectancy is prolonged (Table 2).

There are also data demonstrating that the control of other viruses with effective antiviral therapy, such as human immunodeficiency virus (HIV) and hepatitis B virus (HBV), favorably impact long-term outcomes. Control of HIV RNA levels with long-term highly active antiretroviral therapy (HAART) is associated with a decreased incidence of acquired immunodeficiency syndrome (AIDS), and treatment of patients with chronic hepatitis B and advanced fibrosis with long-term lamivudine therapy to lower HBV DNA levels is associated with decreased liver disease progression rate and a lower incidence of HCC (5).

Sustained Virological Response Persists Long-Term

The earliest and most convincing study demonstrating that a sustained response to antiviral therapy was associated with long-term histological improvement as well as biochemical and virological responses was reported by Marcellin and colleagues from France (6). In this study of 80 patients who had a 6-month sustained biochemical and virological response, mean follow-up of 4 years showed that 93% of patients had a persistently normal alanine aminotransferase (ALT) level and 96% had undetectable serum HCV RNA. A comparison of hepatic histology before and 1 to 6.2 years after completion of interferon therapy showed improvement in 94% of patients, and HCV RNA was undetectable

1 to 5 years after treatment in all 27 patients tested. In an analysis of 4 large trials in which 455 patients achieved a SVR with interferon alfa-2b plus ribavirin and 103 with interferon alfa-2b monotherapy, the actuarial likelihood of maintaining response after a mean 4-year follow-up period ranged from 96% (relapsers who were retreated with interferon alfa-2b plus ribavirin) to 99% (naïve patients who were treated for 48 weeks with interferon alfa-2b and ribavirin) (7). Thus, this analysis of a large study database confirmed that late

treatment biopsies from 4 randomized trials of 10 different regimens using combinations of standard interferon, peginterferon, and ribavirin, it was shown that there was a 39% to 73% improvement in necrosis and inflammation (9). In addition, all regimens significantly reduced fibrosis progression rates in comparison to rates before treatment, with the best results noted with peginterferon plus ribavirin (9). In particular, cirrhosis was reversed in 49% of patients with baseline cirrhosis. Six factors were associated with the absence of significant

peginterferon alfa-2b combined with ribavirin slows the natural progression of fibrosis in nonresponders and relapsers as well as sustained responders (9), the study of Cammà et al. (10) showed a reduction in fibrosis only in patients achieving a SVR or having a relapse. A limitation in both studies is the relatively short time between paired biopsies, i.e., before treatment and 24 weeks after completion of therapy.

Incidence of Hepatocellular Carcinoma is Reduced

The Inhibition of Hepatocarcinogenesis by Interferon Therapy (IHIT) Study Group in Japan has been studying the development of HCC in a cohort of more than 3000 Japanese patients with chronic hepatitis C and has demonstrated that interferon therapy reduces the risk of HCC by half including down to one-fifth in biochemical or virological responders, compared with untreated patients (11). A handful of additional studies have confirmed these initial observations. Compatible with the studies cited in the above paragraph, the IHIT Study Group has also demonstrated reduced inflammation and fibrosis in patients with a SVR (12). However, it should be noted that a reduction in the risk of HCC does not necessarily indicate improvement in overall survival, and that interferon is less effective in patients with cirrhosis. In addition, cirrhotic patients tend to be older, and liver-unrelated mortality may be significant and obscure any potential benefit of interferon therapy.

TABLE 2

Antiviral Therapy Favorably Impacts the Natural History of Chronic Hepatitis C

Long-term virological response after SVR: **> 95%**

- Clinical relevance of detection of small amounts of HCV RNA uncertain

Fibrosis progression rate: **slowed**

- Evidence of reversal of fibrosis, including early cirrhosis

Incidence of hepatocellular carcinoma: **reduced**

- Especially among patients with SVR

Life expectancy and survival: **improved**

relapse is rare in patients who remain HCV RNA negative 6 months after completion of interferon-based therapy. Multiple other smaller studies, including one study with a 10-year mean follow-up (8), showed that SVR predicts a high likelihood of long-term sustained biochemical and virological responses.

Fibrosis and Inflammation are Improved

In a pooled set of data from 3,010 naïve hepatitis C patients with pretreatment and post-

fibrosis after treatment: baseline fibrosis stage, SVR, age < 40 years, body mass index < 27 kg/m², no or minimal baseline activity, and HCV RNA level < 3.5 million copies/mL. Another study evaluating the results of peginterferon alfa-2a monotherapy by analyzing pretreatment and posttreatment liver biopsies from 1,013 naïve patients in 3 randomized trials also showed that antiviral therapy significantly reduced fibrosis, which was closely related to virological response (10). In contrast with the Poynard study that suggested that

Life Expectancy is Prolonged

It would be expected that long-term persistence of a SVR, improvement in fibrosis and inflammation, and a reduced incidence of HCC would translate into a prolonged life expectancy. In fact, recent studies with sufficiently long follow-up are now reporting this ultimate end-point of antiviral therapy (13-16). In a retrospective cohort study of 7 university hospitals and 1 regional core hospital in Japan, 2,889 patients with biopsies, including 2,430 patients receiving interferon and 459 untreated patients were analyzed (13). Compared with the general population, overall mortality was high among untreated patients but not among the treated patients. In the interferon-treated patients, the risk of liver-related death was reduced compared with untreated patients, while the risk of liver-unrelated death remained unchanged. In another study of 459 patients followed for a mean of 8.2 years, multivariate regression analysis revealed that interferon treatment decreased the risk ratio for overall death and liver-related death, particularly in patients with a SVR (14). Once again, interferon showed no association with liver-unrelated death. Another retrospective cohort study of 2,954 patients, including 2,698 who were treated and 256 who were untreated, showed similar results (15). Over a mean 6-year follow-up, interferon therapy improved survival in chronic hepatitis C patients showing a biochemical as well as a virological response by preventing liver-related deaths. Finally, a prospective

cohort 6.8-year follow-up study of 345 patients with cirrhosis, of whom 271 were treated and 74 not treated, showed that interferon inhibited the development of HCC and also improved survival (16).

Conclusions

Thus the above data, which still should be considered preliminary, consistently shows that interferon-based therapy, particularly among those achieving a SVR, is associated with long-term persistence of a SVR, improved fibrosis and inflammation scores, reduced incidence of HCC, and prolonged life expectancy (Table 2). The majority of these results were reported with standard interferon therapy, and the long-term results of peginterferon plus ribavirin therapy with a higher likelihood of a SVR should have a yet greater impact on the population of treated patients with chronic hepatitis C. In summary, antiviral therapy appears to favorably influence the long-term natural history of chronic hepatitis C, with the provision that yet longer follow-up is still needed to better define late natural history after completion of antiviral therapy, particularly in patients with advanced fibrosis.

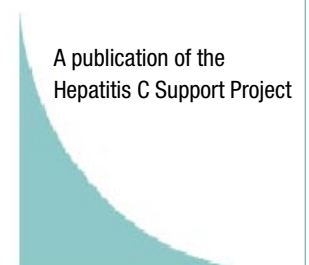
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The Mission of the Hepatitis C Support Project is to offer support to those who are affected by the hepatitis C Virus (HCV), hepatitis B Virus (HBV) and HCV coinfections.

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