PEGINTERFERON ALFA-2a AND RIBAVIRIN IN PATIENTS WITH CHRONIC HEPATITIS C WHO HAVE FAILED PRIOR TREATMENT

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The first study to be completed and published from the HALT-C trial appeared in the April 2004 issue of *Gastroenterology* (volume 126, pages 1015-1023*)*. This study described the results of what we call the "lead-in phase" of the trial; the retreatment of patients with peginterferon alfa-2a (Pegasys) and ribavirin. Prior to starting the HALT-C trial, the only available treatments for patients with chronic hepatitis C virus (HCV) were either standard interferon administered three times weekly or the combination of standard interferon and ribavirin. Unfortunately, many of the patients who had been treated with these medications in the past failed to respond and continued to have chronic hepatitis C, including all patients enrolled into the HALT-C trial. We refer to such patients as non-responders. Shortly before the HALT-C trial began, the combination of peginterferon and ribavirin was shown to be a more effective treatment for chronic hepatitis C than either standard interferon or interferon and ribavirin. The investigators who developed the HALT-C trial recognized that some non-responders who failed to respond to either one or both of these older, less effective therapies could potentially respond to peginterferon and ribavirin, become hepatitis C virus undetectable and achieve a sustained virologic response (SVR). Patients with SVR have no evidence of hepatitis C virus in their body and are believed to be cured of HCV infection. The lead-in phase was therefore designed to provide patients who enrolled in HALT-C the opportunity to achieve an SVR. Data generated by the lead-in phase of HALT-C could also be utilized to identify characteristics of non-responders associated with successful retreatment and SVR. This information could then be utilized by physicians worldwide to determine if their non-responding

patients were likely to benefit from retreatment with peginterferon and ribavirin. More importantly, this information could identify those patients who were very unlikely to respond to retreatment and save these patients the side effects and disappointment of another course of failed therapy.

Data collected from the first 604 patients enrolled in the HALT-C trial between August, 2000 and December, 2001 were included in this report. Sixty-four percent of the patients had been previously treated with interferon and ribavirin. The mean age of the group was 50 years, 73% were male and 77% Caucasian. The average estimated duration of HCV infection was 27 years; 89% were infected with HCV genotype 1. Three-quarters of the patients had more than 1.5 million international units per mL (IU/mL) of hepatitis C virus particles (the HCV RNA level) in their blood. Cirrhosis was present on the pre-study liver biopsy in 39%.

All patients who entered the lead-in phase of HALT-C were treated with peginterferon and ribavirin for 20 weeks. Those patients who still had HCV RNA present in their blood, even in small amounts, entered the maintenance phase of the HALT-C trial. These patients were selected at random to either stop ribavirin and receive a lower maintenance dose of Pegasys for the next 3.5 years or to stop both peginterferon and ribavirin and be followed for the same length of time in the control group without additional therapy. However, those patients who responded to retreatment with Pegasys and ribavirin and had no evidence of HCV RNA at week 20, continued to receive this treatment for a total of 48 weeks. The treatment was then discontinued, and patients were monitored to see if they developed SVR or if they had a relapse with return of HCV RNA.

Thirty-five percent of patients responded to retreatment and had no evidence of HCV RNA at week 20. Unfortunately, many of these patients relapsed after treatment was discontinued. However, 18% of the 604 patients did achieve SVR and remain cured of chronic hepatitis C to this day. The chance of achieving SVR according to several characteristics is listed in TABLE 1. Several years ago it was recognized that African Americans have a much

lower rate of SVR compared to patients of other races. The same was true following retreatment with peginterferon and ribavirin. Only 6% of African Americans achieved SVR following retreatment. The reason why African Americans with chronic HCV respond so poorly to interferon therapy remains unknown but is currently being addressed in another NIH sponsored trial called VIRAHEP-C. Non-African American patients without any of the favorable characteristics associated with SVR also had a very poor chance of achieving SVR with retreatment. For example, SVR was achieved in only 6% of non-responders who were previously treated with interferon and ribavirin and had cirrhosis, HCV genotype 1 and an HCV RNA level of greater than 1.5 million IU/mL.

Many patients experienced side effects of peginterferon and ribavirin which required that the dose of either one or both of these medications be reduced or discontinued. We carefully evaluated the effect that this had upon the ability of patients to achieve SVR. Reducing the dose of ribavirin from more than 80% to less than 60% of the starting dose (for example from 1,000 mg/day to less than 600 mg/day) during the first 20 weeks of treatment was associated with a significant decline in SVR; from 21% to 11%. Reducing the dose of peginterferon within the first 20 weeks had little impact on SVR. However, if the dose of either peginterferon or ribavirin was reduced after week 20, when HCV RNA was already undetectable, the ability to achieve SVR was not affected.

The results from the “lead-in” phase of the HALT-C trial have provided valuable insight into how physicians should management patients with chronic hepatitis C. Non-responders with cirrhosis, genotype 1 and an HCV RNA level of greater than 1.5 million IU/mL are unlikely to respond to retreatment. In contrast, patients with genotypes 2 or 3, levels of HCV RNA less than 1.5 million IU/mL and no cirrhosis have a reasonable chance of achieving SVR and should be considered good candidates for retreatment with peginterferon and ribavirin.

TABLE

CHARACTERISTICS AND SUSTAINED VIROLOGIC RESPONSE

	Sustained Virologic response
Prior treatment:	
Interferon alone	28%
Interferon and ribavirin	12%
Race and Ethnicity:	
Caucasian	20%
African American	6%
Hispanic	18%
Other	33%
HCV genotype:	
1	14%
2	65%
3	54%
Others	17%
Baseline HCV RNA:	
greater than or equal to 1.5 million IU/mL	15%
Less than 1.5 million IU/mL	27%
Cirrhosis:	
Yes	11%
No	23%