



A NEWSLETTER FOR THE HALT-C TRIAL

HALT-C NEWS

Hepatitis C Antiviral Long-term Treatment against Cirrhosis

April 2006

Volume 6, Number 2

HALT-C Accomplishments and Future Directions

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As we approach the final year of the HALT-C Trial, all of the physicians, nurses, and the many others who work behind the scenes organizing and analyzing all of the data you helped generate would like to thank all of you, our patients, for participating in this landmark study. Some of you have already completed 4 years in the HALT-C Trial. For many others, this is your final year. This letter will summarize many of the accomplishments we have already made during the past several years. In addition, we would like to make you aware of exciting plans we have for extending the HALT-C Trial for several additional years and the possibility that we could obtain and evaluate the newest oral anti-viral medications for treating chronic HCV during this next phase of HALT-C.

The primary goal of the HALT-C study is to determine the effectiveness and safety of peginterferon maintenance therapy in patients with chronic HCV and advanced fibrosis or cirrhosis. This study, which took more than a year to design, is a unique collaboration between the National Institutes of Health (NIH); 11 University Medical Centers; a center which collects, manages and analyzes all of the data; and the Hoffmann-La Roche Pharmaceutical Company. HALT-C is not just one large treatment study. A large number of smaller ancillary studies are also being conducted to increase our knowledge and understanding about hepatitis C and its treatment.

HALT-C is now in its sixth year, with one more year to go until it is finally completed. Much has been accomplished since the study began. This could not have been accomplished without your

help and participation. Nine scientific articles have been published to date. Several others will be published within the coming months and years. These include:

- HALT-C is the first study to define how many patients who previously failed to respond to HCV treatment could benefit by retreatment with peginterferon and ribavirin. A sustained virologic response was obtained in 18% of patients during the Lead-in Phase of HALT-C. Various factors which predicted who was likely to achieve a sustained virologic response were also identified. As a result, we now know which non-responders are likely to respond when retreated with peginterferon and ribavirin.
- A pattern of laboratory abnormalities has been identified which could accurately identify which patients with chronic hepatitis C have cirrhosis and are at risk for having esophageal varices. This may reduce the need to perform liver biopsy and endoscopic procedures in many patients with chronic HCV in the future. Identifying patients with cirrhosis and esophageal varices is important since these patients are at the highest risk to develop complications from hepatitis C.
- A blood test called alphafetoprotein (AFP) is utilized by many doctors to determine if patients with chronic HCV are developing liver cancer. AFP was monitored in all patients during HALT-C. This test was abnormal in a lot of patients who have never developed liver cancer. In addition, this test was normal in about half

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ISSUES OF INTEREST

Current topics from experts in the field

Health-Related Quality of Life in Patients with Chronic Hepatitis C and Advanced Fibrosis

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Chronic hepatitis C (CHC) affects at least 3.2 million Americans and is the major cause of chronic liver disease, cirrhosis and liver cancer in the United States. CHC is typically silent; symptoms and signs are present only in those with severe or advanced disease. Unfortunately, symptoms and poor health-related quality of life (HRQOL) are not always helpful in determining which patients have mild, moderate, or advanced disease. In some patients, symptoms of liver disease do not develop until the onset of advanced cirrhosis or liver cancer. Other patients have marked symptoms of fatigue and weakness, despite having mild disease. Because the majority of treated patients are asymptomatic or only minimally symptomatic at most, improvements in symptoms or quality of life have not been considered reasons for recommending therapy.

In most trials of therapy of hepatitis C, eradication of hepatitis C virus (HCV) and prevention of disease progression have been used as the major determinants of successful therapy. Symptoms and quality of life are not mentioned as even secondary endpoints. A few prospective studies have shown that a sustained virological response (SVR) to therapy of chronic hepatitis C can be associated with significant improvements in quality of life, but many of the patients in the studies had mild disease. However, HRQOL in CHC is of growing importance to patients. Fearing a reduction in HRQOL associated with the adverse effects of treatment, some patients decline antiviral therapy. Others request therapy in hopes that their physical, mental, and sexual functioning will improve as a result.

We studied the HRQOL and sexual health in HALT-C patients, who were asked to complete the SF-36 Health Survey and three sexual health questions at their study visits. The SF-36 asks questions about eight physical and mental health domains. The sexual health questions focus on self-reported sexual functioning, desire, and satisfaction. All patients had moderate or advanced CHC when they enrolled in the HALT-C Trial.

Our analyses confirmed that HRQOL was lower among HALT-C patients than people in the general US population. As shown in Figure 1, our analyses indicated that HRQOL scores are lower in HALT-C patients with advanced disease (cirrhosis) than in those with moderate disease (fibrosis). In addition, having advanced disease was associated with lower sexual summary scores. Other important determinants of lower HRQOL scores included the use of

anti-depressant or anti-anxiety medications, cigarette smoking, and higher depression scores. These associations were not surprising: the common health problems found in patients with CHC, such as depression, diabetes, heart disease and obesity, also may contribute to the poorer quality of life.

As shown in Figure 2, our most important findings were that successful antiviral therapy with peginterferon and ribavirin led to improvement in many physical health domains of HRQOL and in sexual health in 254 HALT-C patients with moderate and advanced disease (178 achieved SVR and 76 relapsed after initially responding to therapy). In contrast, mental health domains of HRQOL showed less improvement. These observations suggest that HCV infection may have minimal effect on mood or emotional states. Although many patients with CHC describe difficulty in thinking, concentrating, and memory, such symptoms may result from other underlying conditions, such as anxiety, depression, or use of psychotropic medications, rather than from HCV infection.

Our analysis also suggested that sexual health is diminished among patients with CHC and that a greater reduction in sexual functioning and satisfaction is associated with more advanced disease. Importantly, sexual health scores improved in patients who achieved an SVR. Overall, our findings suggest that diminished sexual health in patients with chronic hepatitis C can be improved, at least in part, by successful antiviral therapy, even in patients with advanced disease.

In summary, analyses of questionnaires completed by HALT-C patients indicate that HRQOL is decreased significantly in patients with CHC who have moderate or advanced disease. The side effects of current therapy result in further decrements in HRQOL during therapy and are major impediments to the initiation and successful completion of such therapy. Nonetheless, even in patients with moderate or advanced CHC, successful antiviral therapy leads to clinically meaningful, significant improvements in HRQOL. Thus, the rationale for antiviral therapy of chronic hepatitis C should include not only a reduction in progression of liver disease and the development of liver cancer but also an improvement in quality of life.

Figure 1 . HRQOL scores at baseline of the eight scales of the SF-36 Health Survey (n = 1,144).

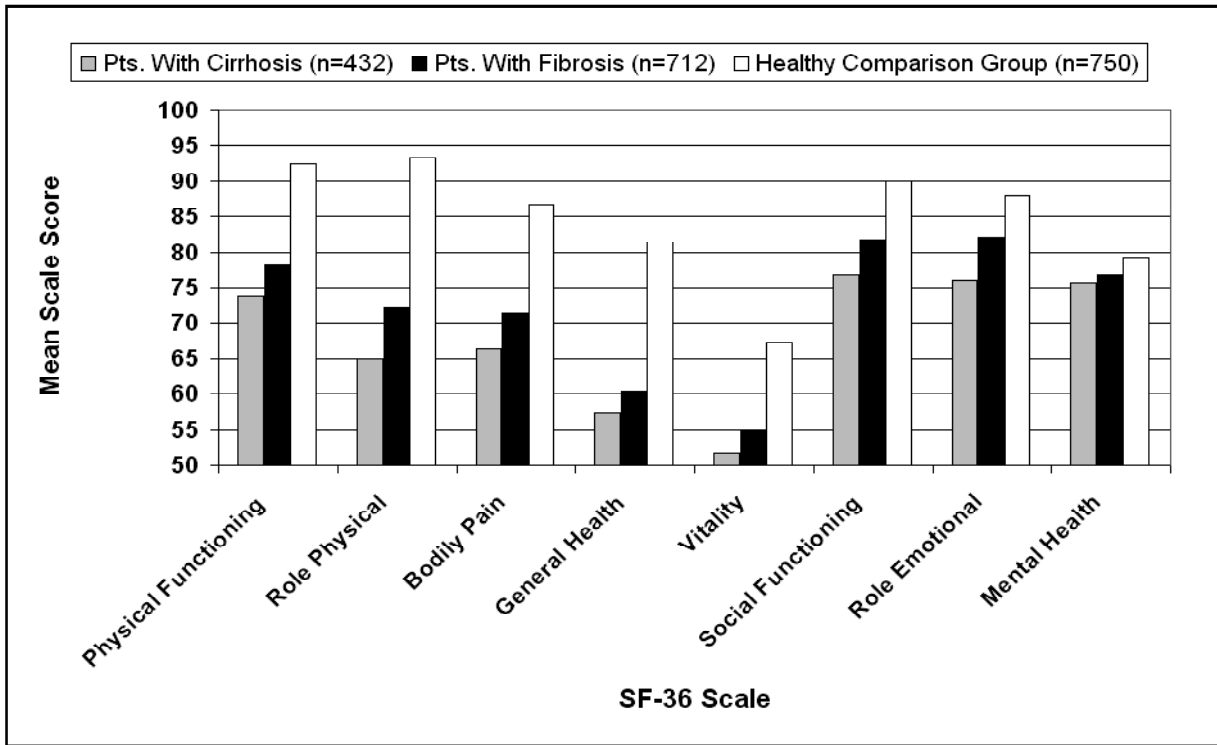
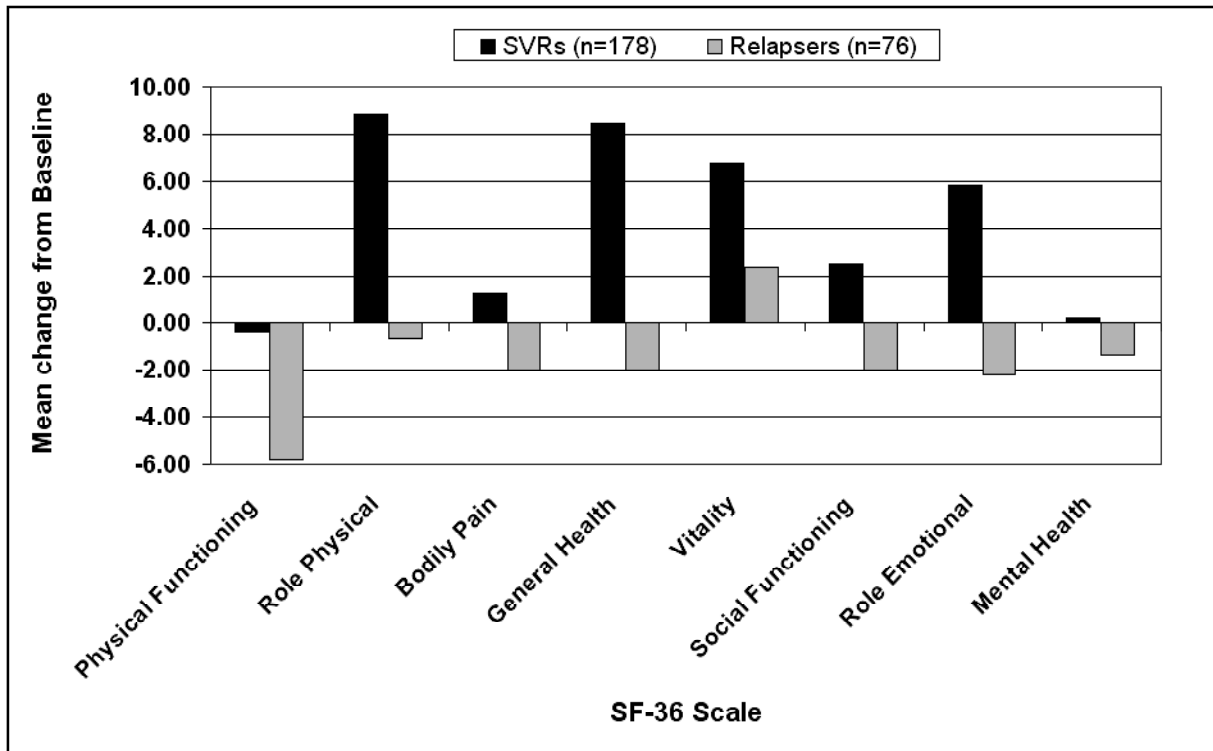


Figure 2. Change from baseline to Week 72 in SF-36 scores by virologic response status (n = 254).



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the patients who did develop liver cancer. These results show that AFP is not such a good test to identify liver cancer in patients with chronic HCV. Other types of blood tests, which may be better markers of liver cancer, are being tested in HALT-C.

- A new test to measure the hepatitis C virus, transcription-mediated amplification (TMA), has been shown to be more sensitive and can detect even lower levels of hepatitis C virus in the blood than previous tests utilized to measure this virus.
- We now better understand how much the dose of peginterferon and ribavirin can be reduced during treatment of chronic HCV without affecting the patient's ability to achieve a sustained virologic response.

As you can see, the HALT-C Trial has generated important information that is already influencing how doctors care for patients with chronic hepatitis C. In the next few years, as this current phase of the HALT-C study comes to a conclusion, we expect to generate even more important results and answer the following additional questions:

- Does long-term maintenance treatment with peginterferon slow the progression of hepatitis C?
- Can long term maintenance treatment with peginterferon prevent the most serious complications of cirrhosis in patients with hepatitis C infection?
- Can long term maintenance treatment with peginterferon reduce the risk of liver cancer?
- Is it safe to take peginterferon for several years, and what is the impact of this medication on the immune system?

As this current phase of the HALT-C Trial comes to an end, we are very aware that many of you still require better treatments for hepatitis C. Fortunately, several very promising oral anti-viral agents have started to be tested in clinical trials. Unfortunately, patients with advanced fibrosis and cirrhosis (such as patients in the HALT-C Trial) are frequently excluded from clinical trials evaluating new medications until these have been

shown to be both effective and safe. For this reason, the leaders of the HALT-C Trial are beginning to develop plans which could extend the HALT-C Trial for several additional years with the hope that we could obtain and provide these new medications for our patients who have participated in HALT-C. We have already had preliminary discussions regarding this possibility with the Food and Drug Administration (FDA) and various pharmaceutical companies. It is currently unclear if and when these new medications will be available for patients in HALT-C. This will depend upon how effective and safe these new medications turn out to be. We will keep you informed of any progress in this area.

Once again we would like to thank all of you for participating in HALT-C. The success of this and any future studies is dependent upon your participation and cooperation. We will continue to offer you outstanding care through the end of the study and keep you informed regarding the possibility of extending this study into the next era and with the next class of medications.



Happy Spring!

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The HALT-C News is a publication of New England Research Institutes and is published periodically.