

A NEWSLETTER FOR THE HALT- C TRIAL

HALT-C NEWS

Hepatitis C Antiviral Long-term Treatment against Cirrhosis

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Hepatic Steatosis (Fat in the Liver)

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Fatty liver disease is fast becoming the most common liver disease in the United States. This is directly related to the increase in obesity in this country. Fat is also commonly found in the liver of patients with hepatitis C and recent studies have suggested that hepatitis C patients who have fat (steatosis) in the liver are more likely to have advanced fibrosis and to have decreased response to interferon and ribavirin treatment. These issues were examined in the HALT-C trial. The results of this analysis was presented at the American Association for the Study of Liver Diseases Meeting in 2003 and 2004 are summarized below.

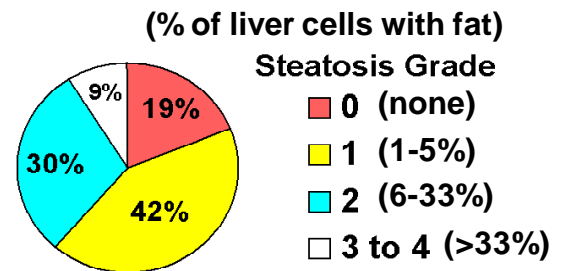
How often is fat found in the liver of HALT-C patients?

Baseline liver biopsies from 1145 patients enrolled in the Lead-in phase of the HALT-C trial showed that 39% of patients had fat in the liver (grade 2-4) (Figure 1). Compared to those with no fat in the liver, HALT-C patients with fat in the liver were more likely to be obese and diabetic, and to have insulin resistance and high triglyceride levels. These metabolic abnormalities are also commonly found in patients with fatty liver disease. Our results indicate that metabolic abnormalities are the main cause of fat in the liver among HALT-C patients. We also found that fat in the liver was more common in patients infected with genotype 3 hepatitis C virus (58%) than those infected with other genotypes (39%) indicating that genotype 3 hepatitis C virus may have a direct effect on fat metabolism in the liver.

Does fat in the liver of patients with hepatitis C result in worse liver disease?

Fatty liver disease, in the absence of hepatitis C, can progress to cirrhosis and liver failure. In the HALT-C study, patients with fat in the liver were more likely to have cirrhosis indicating that the presence of fat in the liver may increase the rate of fibrosis progression.

Prevalence of Hepatic Steatosis



What is insulin resistance?

Insulin is a hormone that regulates glucose and fat metabolism. Patients with insulin resistance require higher levels of insulin to maintain normal blood glucose levels, because insulin is not able to carry out its functions effectively. Response or resistance to insulin can be estimated by simultaneously checking fasting blood glucose and insulin levels. Insulin resistance is the most common underlying abnormality in patients with diabetes and in those with fatty liver disease.

How often is insulin resistance found among patients in the HALT-C trial?

More than 90% of HALT-C patients had some degree of insulin resistance at entry into the trial. This may be related to the high percent of patients with obesity and diabetes. In the HALT-C trial, patients with insulin resistance were more likely to have fat in the liver and to have cirrhosis.

Is response to interferon and ribavirin therapy affected by fat in the liver?

HALT-C patients with fat in the liver had a lower rate of virological response (undetectable hepatitis C virus) during treatment with interferon and ribavirin (Figure 2).

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ISSUES OF INTEREST

Current topics from experts in the field

MOOD AND BRAIN FUNCTION IN THE HALT-C TRIAL

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Many side effects are reported in patients receiving pegylated interferon and ribavirin including fatigue (50%), headache (50%), and nausea (20%). In addition, as many as 50% of treated patients may develop changes in their emotional status or in how they feel including symptoms of depression, anxiety, and irritability as well as difficulty sleeping, concentrating, and thinking. From prior experience, we know that many of these side effects improve with dose reductions or use of anti-depressants, sleep aids, or counseling. However, we currently are unable to reliably predict individuals who are at high risk for these side effects and our ability to prevent or treat these symptoms is limited without a scientific understanding of how and why they develop. Therefore, all patients enrolled in the HALT-C trial are being carefully and continuously assessed for psychiatric and other side effects at and between each study visit by their doctors and nurses. All patients are also asked to complete a depression survey (the Beck Inventory) at each study visit as well as an annual quality of life questionnaire (SF-36) to see how they are doing.

In order to improve our understanding of this problem, HALT-C patients enrolled at the University of Michigan (UMICH) and University of Southern California Los Angeles (USC) are eligible to participate in an ancillary study of the cognitive and mood effects of hepatitis C and its treatment. In this study, participants undergo formal testing of brain function (i.e. cognitive tests) by completing a series of interactive tests administered by trained neuropsychologists before entry, at randomization, and annually during the randomized phase. The preliminary analysis of the pretreatment data shows that very few HALT-C patients are depressed at enrollment. In addition, the lifetime history of depression and anxiety in HALT-C patients is similar to that expected in the general population. However, the lifetime frequency of substance abuse disorders from alcohol and illicit substances is markedly higher in HALT-C patients (~50%) compared to the general US population (~20%). This finding is not unexpected since illicit drug use is the most commonly identified risk factor for acquiring hepatitis

C and chronic and excessive alcohol use have been associated with more rapid disease progression.

The pretreatment cognitive data demonstrates that approximately one-third of HALT-C patients have evidence of mild cognitive impairment that does not appear to be related to the severity of their liver disease or prior substance abuse or psychiatric history. The impairment noted is generally mild and primarily affects an individual's recall of words, attention, and concentration. The speed and processing of visual information, decision making, and word finding abilities of HALT-C patients appears to be similar to that noted in the general population. As in other studies, a patient's general fund of knowledge and information appears to be a strong predictor of cognitive test scores. In addition, subjects who have depressive symptoms at enrollment also appear to have lower cognitive test scores. Preliminary analysis suggests that cognitive test results do not appear to correlate with quality of life scores.

Once these analyses are completed, there are plans to determine the impact of pegylated interferon and ribavirin on the mood status and cognitive function of patients enrolled at UMICH and USC who were treated in the Lead-in phase of the study as well as those subjects who were treated for 48 weeks in the responder phase of the trial. Blood samples to assess markers of depression will also be analyzed from UMICH patients to determine if we can better understand the biological basis for depression and mood changes. At the University of Connecticut, studies of the entire HALT-C population are also underway to determine if there may be a genetic factor linked to serotonin metabolism which may contribute to depressive symptoms during treatment. The lead investigators in the HALT-C cognitive ancillary study (Drs. Fontana, Lok, Bieliauskas, and Kronfol at UMICH and Drs. Lindsay and Back-Madruga at USC) would like to personally thank all of the patients who are participating in this important study for the valuable information and data they are providing to help improve the understanding and management of hepatitis C patients in our study and worldwide.

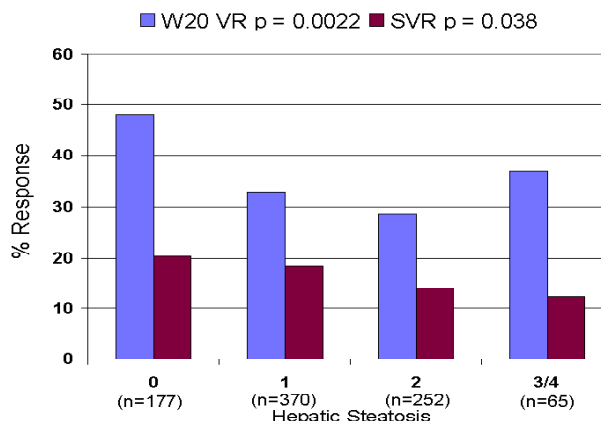
“Hepatic Steatosis” Continued

This effect of fat within the liver on the virologic response to interferon and ribavirin therapy was observed regardless of hepatitis C genotype.

What is the meaning of these findings?

Fat in the liver is a common finding among Americans, not just in patients with fatty liver disease but also in patients with hepatitis C. Fat in the liver can increase the rate of disease progression and decrease the rate of response to interferon therapy in patients with hepatitis C. Weight reduction and better control of diabetes are good for the heart and the liver. In patients with hepatitis C, reducing the amount of fat within the liver may slow down the progression to cirrhosis and increase the chance of viral response to interferon and ribavirin therapy.

Hepatic steatosis and response to antiviral therapy



Impact of Cirrhosis On Response to Antiviral Treatment

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In the Lead-in phase of HALT C, you were treated with the combination of peginterferon plus ribavirin. The main goal of this treatment was to clear hepatitis C; to achieve a sustained virologic response (SVR). SVR is particularly beneficial to patients with more advanced fibrosis or cirrhosis because the liver fibrosis may stabilize or diminish and, in patients with cirrhosis, SVR may be associated with reduction in risk for clinical deterioration or liver cancer (hepatocellular carcinoma). For these reasons we carefully examined the rates of viral response in relationship to severity of the liver disease at the initiation of treatment. This analysis indicates that patients with cirrhosis are less likely to achieve SVR than patients with less severe fibrosis.

Prior to our study, other studies had suggested that cirrhosis may impair response to treatment. Previously published studies of patients with chronic hepatitis C who were treated for the first time with interferon or peginterferon alone (monotherapy) or in combination with ribavirin have included few patients with advanced fibrosis or cirrhosis. One study specifically examined the effectiveness of peginterferon alfa-2a monotherapy in patients with advanced fibrosis or cirrhosis (Heathcote et al., NEJM 2000; 343:1673-1680). In these previous studies, patients with cirrhosis generally had 5 to 10% lower SVR compared to patients with fibrosis. SVR in patients with cirrhosis ranged from 5 to 10% when treated with interferon monotherapy for 24 weeks, to 50% (41% in genotype 1 and 73% in genotypes 2 & 3) when treated with peginterferon alfa-2a plus ribavirin for 48 weeks. The Lead-in phase of the HALT-C trial used the latter combination treatment.

When patients who did not achieve SVR were retreated with peginterferon plus ribavirin, SVR rates ranged from 5

to 18% in published studies. In the HALT-C trial, 18% of patients achieved SVR; 28% in those whose prior treatment was interferon monotherapy, but only 12% in those whose prior treatment was interferon plus ribavirin. In a published HALT-C article, SVR was 11% in 233 patients with cirrhosis, significantly lower than the 23% SVR rate in 371 patients with fibrosis (Shiffman et al., Gastroenterology 2004; 126:1015-1023).

In November 2004, we reported results for all 1,045 patients enrolled in the Lead-in phase of HALT-C, at the annual meeting of the American Association for the Study of Liver Diseases. 391 of these patients had biopsy-proven cirrhosis. Four subgroups were defined with increasing severity of liver disease based upon biopsy stage and platelet counts. SVR declined with increasing severity of disease.

- Group A had least severe disease and SVR of 23% (no cirrhosis on biopsy and platelet count greater than 125,000/ μ l).
- Group B had SVR of 17% (no cirrhosis on biopsy and platelet count of 125,000/ μ l or less).
- Group C had SVR of 10% (cirrhosis on biopsy and platelet count greater than 125,000/ μ l).
- Group D had the most severe disease and SVR of 9% (cirrhosis on biopsy and platelet count 125,000/ μ l or less).

Other predictors of SVR, such as age, gender, genotype, race, high viral load, and type of prior therapy were evenly distributed across the four subgroups so did not account for the decline in SVR from Group A through Group D. We concluded that advanced fibrosis and cirrhosis interfered with the response to antiviral therapy.

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"Impact of Cirrhosis" Continued

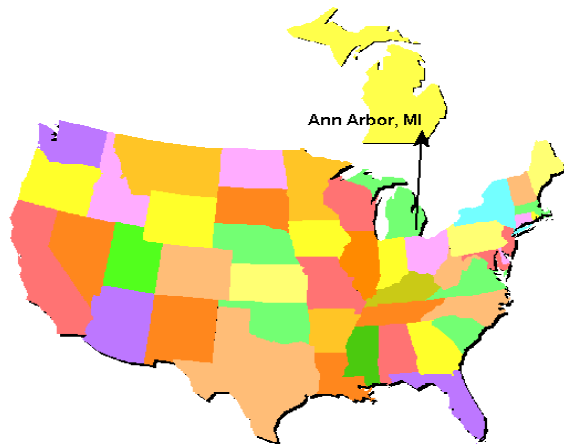
When patients required dose reductions in peginterferon or ribavirin, response to antiviral therapy was further compromised. In our analysis of HALT-C patients, dose reductions reduced SVR rates only in patients with cirrhosis.

Although treatment of chronic hepatitis C has greatly advanced, less than 50% of patients with cirrhosis will respond to initial therapy. In HALT-C patients with cirrhosis who did not achieve SVR after one course of antiviral therapy, retreatment with peginterferon plus ribavirin yielded SVR of only 10%. Therefore, many patients will need additional options for therapy. The most promising approach, maintenance therapy to halt disease progression, is currently under investigation in large clinical trials such as HALT-C.

Although treatment of chronic hepatitis C has greatly advanced, less than 50% of patients with cirrhosis will respond to initial therapy. For those who relapse or fail to respond, retreatment of persons with cirrhosis with peginterferon plus ribavirin yields SVR of only 10% (HALT C). Therefore, many patients will need additional options for therapy. The most promising approach, maintenance therapy to halt disease progression, is currently under investigation in large clinical trials such as HALT C.

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Recruitment and Randomization Update

Enrollment into the HALT-C Trial ended in June 2003, and the last patient was Randomized in August 2004. Here are some final recruitment numbers.

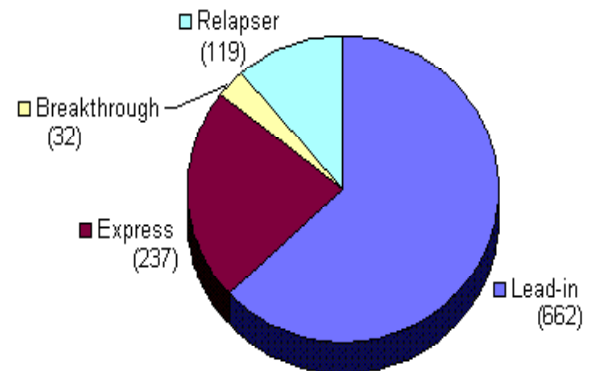
Screening & Enrollment

- 1,824 Patients screened
 - 1,432 for Lead-in phase eligibility
 - 298 for Express eligibility
- 1,382 Enrolled
 - 1,145 as Lead-in patients
 - 237 as Express patients

Randomization

- 1,050 Patients randomized
 - 662 at end of Lead-in Phase
 - 237 as Express Patients
 - 151 after breakthrough or relapse during the Responder Phase

HALT-C Randomized Patients



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