



A NEWSLETTER FOR THE HALT- C TRIAL

HALT-C NEWS

Hepatitis C Antiviral Long-term Treatment against Cirrhosis

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Good Nutrition and Hepatitis C Yoon Park, R.N.



The liver has many functions, one of the most important being its role in performing tasks related to metabolism. The liver processes carbohydrates, proteins, fats, and minerals from the foods that are consumed. The liver

is also responsible for processing and storing sugar, fats, and vitamins until they are needed.

An individual with the hepatitis C virus may experience inflammation or cell damage in the liver. Making wise food choices can protect and nourish a person's liver. A steady intake of a variety of healthy foods including plenty of proteins, fruits, and vegetables is important in keeping the liver as healthy as possible. Here is a quick review of how the liver is involved in metabolizing food and suggestions for healthy food choices:

1. Carbohydrates metabolism: The liver stores sugar and releases it as energy as your body needs it. A damaged liver cannot properly regulate the amount of glucose in the blood and has difficulty in storing glucose. This stored glucose is in the form of glycogen that can then be tapped for an instant energy boost. Without the proper balance of glucose and glycogen, a person with hepatitis C may experience fatigue or hypoglycemia (low blood sugar). Thus, it is important to make good carbohydrate food choices to help your liver with this process. Foods that contain complex carbohydrates such as whole grains, cereals, fruits and vegetables are good choices. Simple carbohydrates should be used only sparingly, if at all. Examples of simple carbohydrates include white flour, sugar, honey, jam, and syrups.

2. Protein metabolism: The liver functions to turn the protein that is consumed into amino acids. The role of amino acids is to help build muscles, tissue healing and repair. Proteins that may be most beneficial include soybeans, legumes, yogurt, low-fat cheese, fish, and lean poultry. The current recommendation is that adults eat 1 to 1.5 grams of protein per kilogram of body weight. However, patients with liver cirrhosis are advised to reduce their protein consumption to 0.6 to 0.8 grams of protein per kilogram of body weight. This is because a high intake of animal based protein from meat may trigger mental confusion due to an excess amount of ammonia. This mental confusion can lead to coma in severe cases.

3. Fat metabolism: The liver makes bile that helps the body to digest consumed dietary fat. Bile is important, as fats cannot be digested without it. A diet high in saturated fats is not recommended as it may cause fatty deposits in the liver which prevent the liver from functioning properly. Overweight individuals with hepatitis C are advised to lose weight and then to maintain a normal weight. Good food choices in this category are monounsaturated fats, found in nuts, seeds, canola and olive oil, and fish. Avoid saturated fats, such as butter, deep fried and fatty foods.

4. Vitamins: Eating a healthy, well-balanced diet can help keep the liver as healthy as possible. The liver has a role in storing the "fat-soluble" vitamins, such as A, D, and E. Your liver also stores other important vitamins, like B12, and releases the vitamins as they are needed. However, too much vitamin A, E (over 400 IU), beta carotene, iron, and niacin can be potentially harmful. Individuals with hepatitis C may wish to talk with their health care provider to determine if using a vitamin or a vitamin/mineral supplement is recommended in their particular situation.

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ISSUES OF INTEREST

Current topics from experts in the field

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 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% of the patients.

All patients who entered the lead-in phase of HALT-C were offered treatment 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 peginterferon and ribavirin and had no evidence of HCV RNA after 20 weeks, 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 manage 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	
<u>Prior treatment:</u>	<u>Sustained Virologic Response</u>
Interferon alone	28%
Interferon and ribavirin	12%
<u>Race and Ethnicity:</u>	
Caucasian	20%
African American	6%
Hispanic	18%
Other	33%
<u>HCV Genotype:</u>	
1	14%
2	65%
3	54%
Others	17%
<u>Baseline HCV RNA:</u>	
Greater than or equal to 1.5 million IU/mL	15%
Less than 1.5 million IU/mL	27%
<u>Cirrhosis:</u>	
Yes	11%
No	23%

“Good Nutrition” continued.

And finally...

- ◆ Avoid alcohol: In order to maintain the best possible liver function, alcohol must not be used. Alcohol is a toxin to the liver and can cause liver damage and cirrhosis.
- ◆ Exercise: Exercise can help keep a body fit and limber. Talk with a health care provider before starting any new exercise program.
- ◆ Drink plenty of fluids: Most people should drink 8 to 12 glasses of water each day. A body needs fluids to carry oxygen and nutrients to its cells. Water also has a role in removing waste from the body.
- ◆ Eat small, frequent meals which may be easier to digest than a big meal. Small meals are also less likely to cause feelings of bloating or fullness.

- ◆ Practice food safety: keep your kitchen’s food preparation areas clean. Wash fresh fruits and vegetable before eating. Store foods properly. Avoid raw or uncooked shellfish.

Still have questions? Talk with your health care provider or your nutritionist about healthy eating and good food choices.



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Evaluation of studies of new chronic HCV treatments

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Since you enrolled in the HALT-C trial, new medications for chronic hepatitis C virus (HCV) treatment have been studied and new ways to use standard interferon and peginterferon have been explored. Information about these studies can be found on various internet medical sites, in HCV support group chat rooms, and in newspapers and magazines. Unfortunately, many of these sources make it seem like a cure for chronic HCV is just around the corner. The reality is that none of the new medications has ever been shown to be more effective than peginterferon and ribavirin, with which you were treated prior to entering the HALT-C maintenance phase.

One of the most important obligations of the HALT-C investigators is to inform you of results from studies evaluating new treatments for chronic HCV. All of the physicians supervising and conducting HALT-C take this obligation very seriously. Previous newsletter issues have reviewed other chronic HCV treatments and available HALT-C results.

We want to make you aware of preliminary results from the COPILOT trial, which studies patients with chronic HCV and advanced fibrosis or cirrhosis, similar to HALT-C. After the first 2 years of treatment in COPILOT, patients who received peginterferon maintenance therapy had fewer internal bleeding episodes than patients treated with colchicine. Patients who developed internal bleeding had slight worsening of their liver disease. However, the number of patients who developed liver cancer, liver failure, required a liver transplant, or died was similar in patients treated with peginterferon maintenance therapy and patients treated with colchicine. Although the early results are exciting, the COPILOT investigators plan to continue their study for another 2 years and have not switched patients from colchicine to peginterferon maintenance therapy.

The HALT-C investigators have carefully examined the COPILOT data and have discussed the results with the HALT-C Data Safety and Monitoring Board (a group of doctors not affiliated with the HALT-C centers whose role is to monitor HALT-C progress and ensure that patients are treated safely and fairly). Our investigators agree that the best way to prove that peginterferon maintenance therapy can benefit patients with chronic HCV is to complete HALT-C as planned. The HALT-C investigators will continue to closely monitor COPILOT and other studies evaluating chronic HCV treatments. As in the past, we will openly discuss this information and your options with you. Thank you for your continued participation in the HALT-C trial.

Therapy for non-responders to pegylated interferon and ribavirin

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Enrollment of patients in the randomized phase of HALT-C is now complete. One thousand and fifty patients have been successfully randomized and the trial has reached the halfway mark. At present patients are beginning to return for their two-year evaluation and liver biopsy. Congratulations to all of you who have volunteered your time and effort to this important endeavor. Those of you who are in the control group may be wondering if it makes sense to continue participating in the study. The answer is an emphatic **YES!** Although new therapies are being developed and tested in patients with chronic hepatitis C, regrettably the "magic bullet" still eludes us. By continuing to participate in the trial you will have the comfort of knowing that you will be closely monitored and you will remain in an environment to receive the latest up-to-date information about progress in the field. The purpose of this brief article is to provide a short overview of the alternative therapies that have been tried for patients who did not respond to combination interferon and ribavirin.

Antiviral Agents

Triple Therapy (Peginterferon, ribavirin and amantadine)

Amantidine is an antiviral agent used to treat infections with influenza A virus. Amantidine showed some promise as a candidate agent against hepatitis C virus in one small study but subsequent trials have been generally disappointing. Nonetheless, amantidine continues to be tested in patients with chronic hepatitis C. A recent analysis of all the different trials using amantidine showed that there was no added benefit of using amantidine with interferon and ribavirin (triple therapy) over interferon and ribavirin in patients who were never treated. In one small, European study, triple therapy was tried for one year in 25 patients who failed to respond to standard based therapy. Only 1 patient had a sustained clearance of virus. In another study, amantidine, peginterferon alfa 2a and ribavirin were compared to peginterferon alfa 2a and ribavirin. No difference was observed in the rates of sustained response between the triple therapy group, 14%, and the combination group, 12%. Of note, the results of re-treatment of non-responders in the HALT-C trial, using pegylated interferon alfa 2a and ribavirin was 18%. Thus at present there does not appear to be any added benefit of using triple therapy if you have failed re-treatment with peginterferon and ribavirin.

BILN 2061

This as yet un-named drug has received a great amount of attention in the press lately. It belongs to a class of drugs called protease inhibitors and functions by blocking an enzyme necessary for viral replication. During the initial testing phase, the drug was administered to 8 patients with genotype 1 virus. An impressive 1000-fold reduction of virus was observed in some patients. However, the virus level quickly rebounded after stopping the drug. In further testing, the drug did not seem to work as well in patients infected with genotypes 2 and 3. Unfortunately, despite a promising start, further testing of this drug in humans has been placed on hold because significant side effects. Two other protease inhibitors are being developed, VX-950 and Sch-7, but they have not been tested in humans as yet.

Interferon Gamma

Despite its name interferon gamma is unrelated to interferon alfa. However both types of interferon need to be administered by injection and have similar side effects. In laboratory studies, several investigators have shown that it possess anti-viral action. Therefore interferon gamma was tested in 14 patients who had either relapsed to or failed combination interferon alfa and ribavirin therapy. Disappointingly, not a single patient had improvement in liver enzymes or a decrease in viral levels. Thus, we cannot recommend interferon gamma as an option for those failing peginterferon and ribavirin.

Ribavirin Like Compounds

Compounds such as levovirin (the mirror image of ribavirin, like left and right hands) and viraclidine (which is converted to ribavirin in the liver) are being developed with the expectation that they will have fewer side effects such as the breakdown of red blood cells (hemolysis) and therefore be better tolerated and more effective than ribavirin. Preliminary studies suggest that these compounds are not significantly better than ribavirin and therefore are unlikely to substantially increase rates of sustained viral clearance. Further data and experience is needed on these agents before firm recommendations can be made regarding the most appropriate clinical setting to use them in.

Immunomodulators

Immunomodulators, as the name implies, are a group of small molecules secreted by inflammatory cells that may modulate the immune response. The primary purpose of using these compounds is to decrease inflammation in the liver.

IL-12

IL-12 is a molecule that may enhance the immune response towards clearance of viral infections. Some studies suggested that patients with chronic hepatitis C have deficient IL-12 responses and that administration of IL-12 could lead to elimination of the virus. The results of an initial safety study were very encouraging. 50% of patients treated with IL-12 were able to clear virus. This led to a large randomized trial comparing IL-12 to placebo in previous non-responders to interferon monotherapy or combination therapy. Unfortunately the results of the larger study were generally poor. The compound did not work well and a substantial number of patients exhibited significant side effects that required termination of treatment. Further testing of this agent in patients with chronic hepatitis C has been suspended.

IL-10

IL-10 is a cytokine with anti-inflammatory properties. A small pilot study suggested that IL-10 was well tolerated, and could decrease inflammation and scarring in the livers of patients not responding to standard treatment. In a larger trial, non-responder patients received IL-10 for one year. Some improvement in liver inflammation was demonstrated, but viral levels increased during the study period and no patient cleared virus. Several patients developed flares in their hepatitis necessitating withdrawal of the drug. Thus, although the activity of the liver disease improved in some patients there was a small risk of worsening of hepatitis and this treatment cannot be recommended at present.

Thymosin α 1

Thymosin is a small protein that has been shown to stimulate the immune response against viruses. Thymosin is currently being evaluated in 2 large studies as a form of therapy for patients who failed to respond to interferon alone or interferon plus ribavirin. At the moment, there is insufficient data available to recommend thymosin.

Herbal Medicines

Complementary therapies are being increasingly used to treat a variety of medical ailments. Recently, it was reported that a staggering 28 billion dollars was spent on complementary and alternative therapies here in the United States, a sum that

almost equals that spent on conventional Western medicine. Despite the expenditure of this vast sum of money and widespread use none of these therapies have been rigorously evaluated and none are of proven benefit for chronic hepatitis C. A recent study conducted at one of the HALT-C participating centers reported that more than 50% of patients with chronic hepatitis C were using between 3-5 herbal remedies daily for control of their hepatitis C. A recent analysis of the use of 14 medicinal herbs (CH-100, Silybin, Silymarin, Glycyrrhizin, Complete Thymic Formula, Oxymatrine, Bing Gang Ling, Bing Gang Ning granule, Gansu, Bing Gang Capsule, Yi Zhu decoction, Qinggan and Bushen granule, Yi Er Gan Tang) concluded there was insufficient evidence that any them influenced the outcome of infection. One of the more popular compounds, Silymarin, the active ingredient of milk thistle, may reduce liver inflammation but it has not been shown to have any effect on viral clearance. It has not been shown to be harmful to the liver and if you are using this compound it may be safe for you to do so. It is important to be aware that many herbal preparations, especially those obtained from non-reputable sources, may contain impurities or toxins that are harmful to the liver and can be fatal. If you plan to consider using a herbal preparation it is best to first consult with your physician or caregiver.

Promising Therapies?

A number of experimental agents that specifically interrupt the viral life cycle are under consideration for testing in humans. These include antisense oligonucleotides and ribozymes, which either bind to or cleave important regions of the virus and prevent viral replication. At the moment these approaches are still considered experimental and several problems with delivery and safety need to be worked out before they are ready for use in human trials.

General Advice

It is evident from this review that there are few promising agents likely to be available in the near future. What can you do in the meantime? It is important to remember to abstain from alcohol, which will prevent further damage to your liver and other organs. Avoid vitamins that contain excess iron or vitamin A, which can also damage your liver. A balanced diet and a regular exercise program should improve overall well being and help to prevent weight gain which can be harmful to your liver. Regular follow-up and monitoring of your disease including a surveillance program for varices and liver cancer are advised. This may serve to prevent complications of hepatitis C from developing and to determine when a prompt referral for liver transplantation is needed. Keep the spirits up and we look forward to seeing you at the next clinic visit.