



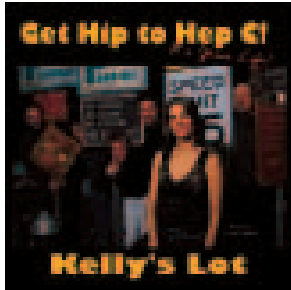
A NEWSLETTER FOR THE HALT- C TRIAL

HALT-C NEWS

Hepatitis C Antiviral Long-term Treatment against Cirrhosis

February 2003 Volume 3, Number 1

“GET HIP TO HEP C!”



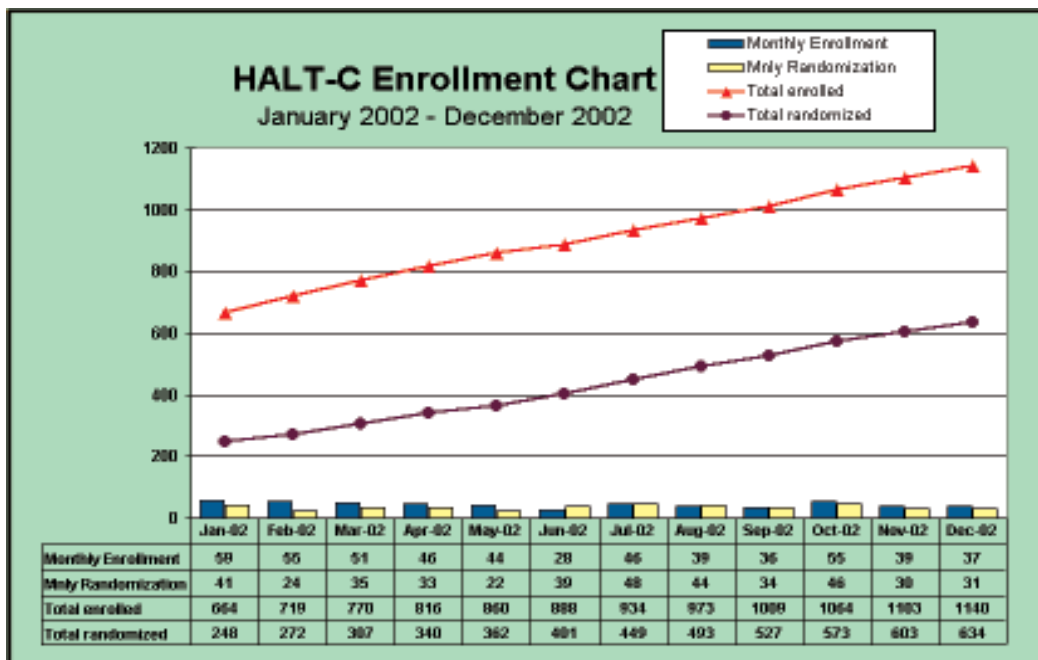
“Get Hip to Hep C,” says Kelly Zirbes, founder and lead singer of the Kelly’s Lot rock band. “Hepatitis C is out there. Let’s all talk about it! Everyone knows someone who has the virus. I want

people to talk about it... without cringing! It’s time to stop the ignorance and start supporting family and friends with hepatitis C.”

Six years ago, Kelly’s lot took on the challenge of playing one gig each month to help a friend with expensive medical bills. From the first show, Kelly’s musical career took a detour. “The music was never going to be enough. It lacked substance. For the first time, to stand in front of everyone with a message, it all made sense to me. It was no longer about self-promotion and playing just for fun or money. It really rocked my boat!”

A few years later, Kelly lost a close friend to hepatitis C. She turned her energies toward raising public awareness about the virus. Since then, Kelly’s Lot performances have turned into “Get Hip to Hep C” fests. As the official band of the American Liver Foundation, Kelly’s Lot recently completed a cross-country benefit tour to get people talking about hepatitis C. “Fear and ignorance have kept a muzzle on Hep C. People are tired of diseases and charities, so we use music to get to them. We hand out *Get Hip to Hep C* CDs instead of pamphlets. A spoonful of sugar helps the medicine go down,” Kelly says. Kelly’s Lot audience is soon rocking and talking about Hep C.

Giving people the courage to talk about hepatitis C is the result of Kelly’s passionate vocation. We at USC are proud of Kelly Zirbes and the Kelly’s Lot band. Rock on!



ISSUES OF INTEREST

Current topics from experts in the field

INITIAL RESULTS FROM THE HALT-C TRIAL PRESENTED AT ANNUAL LIVER MEETING

Karen L. Lindsay, M.D.
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University of Southern California

On behalf of all investigators, staff, patients and NIH personnel involved in the HALT-C Trial, Dr. Mitch Shiffman (PI, Virginia Commonwealth University) presented the initial results from the HALT-C Trial to attendees at the annual Liver Meeting in Boston on November 4, 2002. Data from the first 212 patients who received peginterferon alfa-2a with ribavirin were analyzed to determine the hepatitis C virus (HCV) virologic response rates and factors associated with response. "Virologic response" is defined as a negative blood test for HCV RNA, and indicates that the virus is not replicating or multiplying.

In this patient group who participated in the "Lead-In Phase" of the trial, the average age was 49, 73% were male, 83% were Caucasian, and 9% were African American. Eighty-eight percent were infected with HCV genotype 1. Sixty-two percent had previously received unmodified interferon with ribavirin. The remaining 38% had received unmodified interferon alone. During the first 24 weeks of treatment, only 11 of the 212 (5%) patients dropped out because of treatment side effects.

First, the data were analyzed to determine the percentage of patients who had a virologic response and when that response occurred during the study. Thirty-eight percent of patients had a virologic response at treatment week 20. These patients continued taking peginterferon alfa-2a and ribavirin for a total of 48 weeks of treatment. A small percentage of these patients had a "virologic breakthrough," where the HCV RNA test became positive again despite continuation of treatment. Overall, 75 of the 212 (35%) patients had a virologic response at the end of treatment (week 48). During follow-up off treatment through study week

72, 33 of the 75 (44%) patients experienced a "virologic relapse," where the HCV RNA became detectable again in the blood. Therefore, overall, 42 of the 212 (20%) patients in this initial report developed a "sustained virologic response" (SVR), defined as a negative test for HCV RNA in the blood at the end of treatment and for 24 weeks after treatment is discontinued. In general, patients with SVR are considered to have cleared their HCV infection.

Next, the data were statistically analyzed to identify factors that were associated with response to treatment. Factors that were statistically more likely to be associated with SVR were: (a) previous treatment with interferon alone, compared to interferon and ribavirin; (b) infection with HCV genotype 2 or 3, compared to genotype 1; and (c) Caucasian race, compared to African American race.

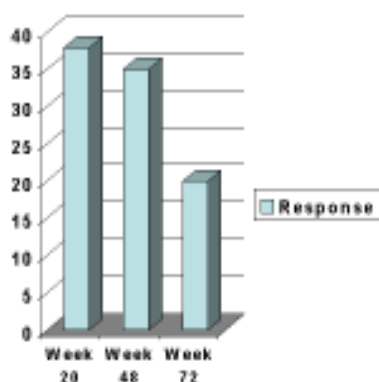
When we have discussed these findings with our patients at USC, they have asked many important questions. Here are answers to four common ones:

1. *Why is the HALT-C SVR rate so low, at only 20%, when I have heard that peginterferon with ribavirin treatment is associated with much higher SVR rates?* Higher SVR rates are seen in HCV patients who have never been treated. One recent study showed that among patients who receive peginterferon alfa and ribavirin as their first therapy, fewer patients infected with genotype 1 (46%) developed SVR than those infected with genotype 2 or 3 (76%). The HALT-C Trial was specifically designed for patients who did not respond to previous interferon therapy, which is an indication that their viral infection was more resistant to interferon therapy. At the time the HALT-C Trial was designed, peginterferon was still an investigational treatment. However, because there was evidence that it was more effective than unmodified interferon, the HALT-C study was designed so all patients could have the opportunity to receive peginterferon therapy. We hoped that the long-acting peginterferon combined with ribavirin would be more effective in clearing HCV.

2. *Why was the SVR rate higher in patients who had previously received interferon alone without ribavirin?* Other studies have shown that interferon combined with ribavirin therapy was generally more effective than interferon alone. All patients who participated in the "Lead-In Phase" of the HALT-C Trial received both peginterferon alfa-2a and ribavirin. Therefore, patients who had previously been treated only with unmodified interferon received two new and potentially more effective agents in the HALT-C Trial (peginterferon and ribavirin). However, patients previously treated with unmodified interferon and ribavirin received only one new

HALT-C Trial: Initial Results

- Treatment week 20 response: 38%
- End-treatment week 48 response: 35%
- Sustained (week 72) virological response: 20%



and potentially more effective agent in the HALT-C Trial (peginterferon).

3. *Why do African American patients respond to treatment at a lower rate?* This question addresses the fundamental issues regarding response to interferon-based therapies for hepatitis C. Unfortunately, the precise mechanisms by which interferon and ribavirin work to reduce the levels of HCV RNA or clear the virus are still not known. Questions regarding the mechanisms of virologic response are being addressed in several laboratory-based HALT-C ancillary studies. We believe that the mechanisms involve complex interactions between the infecting virus and the patient's immune system, which is controlled and modified by the patient's genetic background and potentially other disease-related or environmental factors. An overall SVR rate of 20% to retreatment in the HALT-C Trial, then, is easier to understand since the virus and patient remain the same and the only new factor is one or two new treatment agents. The lower response rate in African Americans, which has been seen in previous treatment trials, is the focus of other ongoing research projects as well.

4. *Why did so many patients' infection respond to treatment by week 48 and then relapse?* This question addresses the fundamental issue of hepatitis C viral clearance with interferon-based therapy. In patients who experience virologic relapse, we think that hepatitis C is being suppressed to such an extremely low level with treatment that HCV RNA cannot be detected despite very sensitive blood tests. However, some cells are obviously still infected with HCV, allowing the virus to reappear in the blood when treatment is stopped. A very important question for ongoing research is how and why these treatments are able to suppress but not clear the virus from all infected cells in the body..

How have these results affected the HALT-C Trial? The Steering Committee of the HALT-C Trial meets monthly to review the study design, conduct, and results. Because some Lead-In patients were experiencing virologic breakthrough and relapse after initially responding, the Steering Committee amended the protocol in 2001 to allow these patients to be randomized into the long-term phase of the study. This means that every Lead-In patient in the HALT-C Trial who does not develop SVR is eligible to continue participation in the long-term study. Additionally, in order to evaluate whether the HALT-C Trial continues to offer the best study design, the Steering Committee also discusses results from other hepatitis C treatment trials. When another peginterferon (peginterferon alfa-2b, PEG-Intron™) was FDA-approved, the Steering Committee amended the protocol to also allow patients who did not respond to PEG-Intron with ribavirin to be randomized into the long-term phase of the HALT-C study.

Many patients have been inquiring about new drugs for hepatitis C that they have heard about in the news or through the Internet. For example, the FDA approved peginterferon alfa-2a (Pegasys®) for treatment of chronic hepatitis C on October 16, 2002. Patients have felt very reassured when we confirm that they have already received Pegasys as a

patient in the HALT-C Trial!!

Several agents are currently in early stages of testing as potential treatments for hepatitis C. In general, these agents fall into two categories—antiviral agents (drugs designed to specifically target the ability of the virus to replicate) and agents aimed at reducing the amount of inflammation and fibrosis (scar tissue) in the liver without affecting the virus. The first studies using a specific antiviral agent (BILN 2061) in patients with hepatitis C were presented at the November Liver Meeting in Boston. A temporary reduction in levels of HCV RNA was seen in the 33 patients who received the drug. Although promising, these results are extremely preliminary because patients were treated for only two days and levels of HCV RNA rapidly rose again when the drug was discontinued. It will take several years for larger studies to determine whether (a) the drug effects can be sustained, and (b) the drug is safe when taken for a longer period of time.

In the HALT-C Trial, Pegasys is being evaluated as an agent aimed at reducing the amount of inflammation and fibrosis in the liver. Many other agents that target liver inflammation and fibrosis are at very early stages of testing. The HALT-C Steering Committee will also continue to monitor the results of these studies in order to ensure that our trial remains the best available study for our patients.

We greatly appreciate all the hard work of the staff and patients involved in the HALT-C Trial. We hope you are proud of the results you have helped generate. Together we will continue to ask questions and seek answers toward our shared goals: finding safe and effective therapy for patients with hepatitis C and understanding why and how these treatments work.

Scientific journal references:

Initial HALT-C results: *Hepatology* 2002; Volume 36, Abstract 295A.

Other hepatitis C findings: *Hepatology* 2002; Volume 36, Abstracts 304A and 379A; and the *New England Journal of Medicine* 2002; Volume 347, pages 975-982.

HALT-C Trial: Initial Results Treatment Response Definitions

- Virologic Response: negative blood test for HCV RNA
- Virologic Breakthrough: virologic response on treatment followed by loss of virologic response despite continuation of treatment
- Virologic Relapse: virologic response at the end of treatment with loss of response after treatment discontinued
- Sustained Virologic Response (SVR): virologic response at the end of treatment and for 24 weeks after treatment is discontinued

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AFP	CT	INTERFERON
ALT	DOC	JAUNDICE
ANTIGEN	ENDOSCOPY	KELLYS LOT
ASCITES	FATIGUE	LIVER
AST	FDA	LIVER BIOPSY
BILE	FIBROSIS	MEDS
BLOOD	HALTC	MDS
CIRRHOSIS	HALTCTRIAL.ORG	NURSE
CLINICAL TRIAL	HEALTH	PEG

ABOUT THE UNIVERSITY OF SOUTHERN CALIFORNIA



Los Angeles was little more than a frontier town in 1885 when USC founded the School of Medicine. Today, the Keck School of Medicine of USC has more than 960 full-time and 3700 voluntary faculty who serve more than 1 million patients annually in 14 affiliated hospitals. The Los Angeles County USC Medical Center, located on USC's Health Sciences Campus, is the nation's largest medical teaching facility and amongst the largest trauma care centers. With its more than 900 interns and residents and 1,600 member voluntary staff, the County Hospital covers virtually every medical specialty. The Center has handled as many as 900,000 emergency room and outpatient visits, and nearly 57,000 admissions. All of the HALT-C Trial patient visits are conducted at the GCRC, General Clinical Research Center, at LAC-USC. The GCRC was opened at USC in 1961.

HEPATITIS WORD SEARCH

C	L	I	N	I	C	A	L	T	R	I	A	L
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A	T	E	P	O	H	B	I	R	O	T	S	A
F	C	R	E	S	E	A	R	C	H	D	I	A

PEGINTERFERON	RESPONDER	SGOT
PILL	RIBAVIRIN	VARICES
PROTOCOL	RNA	VIRUS
RESEARCH		