HALT-C Overview

Purpose

The **H**epatitis C **A**ntiviral **L**ong-term **T**reatment against **C**irrhosis (HALT-C) Trial is a randomized controlled trial designed to evaluate the safety and efficacy of long-term use of pegylated interferon for the treatment of chronic hepatitis C in patients who failed to respond to previous interferon therapy. The HALT-C Trial was developed to determine whether prolonged interferon therapy altered histological and clinical outcomes in a group of patients who had failed to eradicate hepatitis C virus with previous interferon treatment.

Rationale

Only a limited number of patients with chronic hepatitis C virus (HCV) achieve a sustained virologic response following treatment with interferon or interferon plus ribavirin. Virologic response, following either of these treatments, has been associated with an improvement in liver histology. An improvement in liver histology has also been observed in patients who failed to achieve a virologic response and remained HCV positive during treatment. A recent controlled study has suggested that continuing interferon treatment in these patients may maintain this histologic improvement. Uncontrolled trials suggest that interferon therapy may also reduce the risk for hepatocellular carcinoma (HCC) and improve survival in patients with chronic hepatitis C and cirrhosis.

Study Design

Approximately 1,350 patients with chronic HCV and advanced hepatic fibrosis (Ishak stage 3-6) who have failed to respond to previous treatment with interferon will be enrolled at 10 clinical centers and entered into a Lead-in phase. They will be treated with a combination of pegylated interferon (Pegasys®, Hoffmann-La Roche) 180 mcg/week and ribavirin (1,000-2,000mg/day) for 24 weeks. Patients who have no detectable HCV-RNA at week 20 will continue on combination therapy until week 48.

Patients who do not clear virus will be randomly assigned at week 24 to either continue treatment with pegylated interferon alone (90 mcg/week) for an additional 42 months, or to have treatment discontinued. All patients will be followed at 3-month intervals following randomization. Liver biopsy will be performed at baseline and after 2 and 4 years of treatment. The sample size of 900 randomized patients will provide 90% power to detect a decrease in the annual rate of development of cirrhosis or complications of cirrhosis from 6% per year in the control group to 3% per year in the treated group.

Because of slower than expected enrollment and the approval by the FDA of peginterferon alfa-2b after the start of the trial, we modified the study protocol in three ways (Figure A.1). First, criteria for admission to the trial were liberalized to allow patients to enter the trial with lower platelet and white blood cell counts than had been initially considered safe or tolerable. Second, Lead-in patients and those continuing on therapy after 24 weeks who demonstrated return of viremia during or after their 48-week treatment period (called “Breakthrough” or “Relapse” patients, respectively) were allowed to return to enter the randomized trial. Third, patients treated with peginterferon alfa-2b (or with peginterferon alfa-2a in licensing trials) outside the HALT-C Trial who in other respects met all study criteria, having received the equivalent of Trial Lead-in period therapy, were allowed to enter the long-term trial as “Express” patients.

Those patients who complete Month 48 will be offered an “extended follow-up” visit after their Month 54 study visit at Month 60 and Month 72 through April 2007. These visits will primarily be to identify outcome events, and to provide information to patients concerning the current status of the trial. Some

questionnaires, blood tests, and an ultrasonogram will be performed. This visit is not to take the place of patients establishing a relationship with a primary care or liver specialist physician once the Month 54 visit is completed.

Study Hypotheses

1) In patients with chronic hepatitis C and bridging fibrosis who failed to eradicate the virus with previous interferon therapy, long-term treatment with interferon is safe and can prevent progression to cirrhosis.

2) In patients with cirrhosis secondary to chronic hepatitis C who failed to eradicate the virus with previous interferon therapy, long-term treatment with interferon is safe and can reduce the risks of hepatic decompensation or of hepatocellular carcinoma.

Inclusion and Exclusion Criteria

The following eligibility criteria were evaluated during screening.

Inclusion

- A history of chronic HCV
- Failure to achieve a virologic or biochemical response during previous interferon therapy (with or without ribavirin)
- An elevation in serum AST or ALT within 6 months of enrollment
- At least stage 3 fibrosis on liver biopsy by the Ishak scoring system
- An age of 18 years or greater
- Willingness to utilize adequate contraception when being treated with ribavirin

Exclusion

- Any other co-existent liver disease
- A Child-Turcotte-Pugh Score of 7 points or greater
- A history of ascites, hepatic encephalopathy or variceal hemorrhage
- A platelet count < 75,000, PMN count < 1,500 or Hct < 33%
- An AFP > 200 ng/ml or the presence of a hepatic mass suggestive of HCC
- A bilirubin > 2.5 mg/dl (except for patients with Gilbert's syndrome)
- A serum creatinine > 1.5 mg/dl
- Co-infection with HIV
- Poorly controlled diabetes mellitus
- Another serious medical disorder
- A serious psychiatric disorder
- A history of alcohol abuse within the past year
- The use of illicit drugs within the past two years
- Intolerance to previous interferon treatment
- Inability to provide informed consent
- Pregnancy, breast feeding, or the male partner of a pregnant woman
- Inability or unwillingness to undergo liver biopsy

Outcome Variables

Primary outcome variables to be assessed in the two groups of patients include:

- Development of cirrhosis on liver biopsy (progression of Ishak fibrosis score by 2 points or more)

- Development of hepatic decompensation, as shown by:
  - Sustained increase in the Child-Turcotte-Pugh score to 7 points or higher
  - Variceal hemorrhage
  - Ascites
  - Spontaneous bacterial peritonitis
  - Hepatic encephalopathy
  - Development of hepatocellular carcinoma
  - Death

Secondary outcomes include quality of life, serious adverse events, events requiring dose reductions, and development of presumed hepatocellular carcinoma.

Ancillary Studies

As of December 1, 2004, approved HALT-C Ancillary Studies are listed below with each study's location in Section K of this Manual.

K.1: Immunologic and Virologic Correlates of Liver Fibrosis
K.2: Hepatic Steatosis in Chronic Hepatitis C: Risk Factors and Role in the Development of Hepatic Fibrosis
K.3: Serum Fibrosis Markers in Chronic Hepatitis C
K.4: Cognitive Effects of Long-Term Pegylated Interferon in Patients with Chronic Hepatitis C
K.5: Pre-Study Serial Histology as a Predictor of Responses to Continuous Therapy During the HALT-C Trial
K.6: Quantitative Assessment of Hepatic Function in Chronic Hepatitis C
K.7: Risk Factors for Progression of Liver Disease in Chronic Hepatitis C
K.8: Iron and HFE Mutations in Chronic Hepatitis C
K.9: Bayer Versant bDNA 3.0 Quantification and TMA Detection of HCV RNA for the HALT-C Trial
K.10: Measurement of Serum Des-γ-Carboxy Prothrombin (DCP) for Early Detection of Hepatocellular Carcinoma (HCC) in Patients with Chronic Hepatitis C Virus (HCV) Infection
K.11: Clinical Utilities of AFP-L3 Determination in Early Recognition, Diagnosis and Prognosis of Hepatocellular Carcinoma in Patients with Chronic Hepatitis C
K.12.1: Influence of Host Genes on the Course of Chronic Hepatitis C
K.12.2: Utility of HALT-C Liver Biopsy Samples for Gene Expression Experiments Using Microarray Analysis
K.12.3: Genetic Predictors Of Depressive Symptoms Among Patients Treated With Interferon-α
K.12.4: Genetic Polymorphisms Associated with Non-Response to Treatment of Chronic HCV Infection
K.13: Effects of Interferon on Portal Hypertension Ancillary Study (Discontinued on 11/29/2001)

Manual of Operations Overview

This binder is the Manual of Operations (MOO) of the HALT-C Trial.

Section B includes the protocol, the analysis plan, a description of the policies and procedures, management guidelines, and the visit schedule.

Section C describes the web-based date management system.

Section D describes the trial phases: screening, lead-in, randomized, week 20 responder, and extended follow-up.

Section E includes detailed procedures for specimen collection, processing, and shipping of specimens to the repository. It also describes the Virology Lab Procedures.

Section F includes information sheets to be given to the patients.

Section G describes the procedures of the Pathology Committee.

Section H describes the trial medications, including shipment from Hoffmann-La Roche to the clinical centers, distribution to the patients, and criteria for dose reduction.

Section I describes the procedures for reporting adverse events and clinical outcomes.

Section J describes the QA/QC plan for the Trial.

Section K includes the descriptions of the Ancillary Studies.

Section L describes endoscopy, ultrasound, MRI, and CT procedures for the Trial.

The second binder includes copies of the data forms for the Main Trial, data forms for ancillary studies, and question by question (QxQ) instructions for forms completed at clinical centers.

The second binder also includes procedures for administering the Block food frequency questionnaire and a manual and QxQ instructions for the Composite International Diagnostic Interview (CIDI).

FIGURE A.1: DESIGN OF THE HALT-C TRIAL