



A NEWSLETTER FOR THE HALT- C TRIAL

HALT-C NEWS

Hepatitis C Antiviral Long-term Treatment against Cirrhosis

July 2001

Volume 1, Number 2

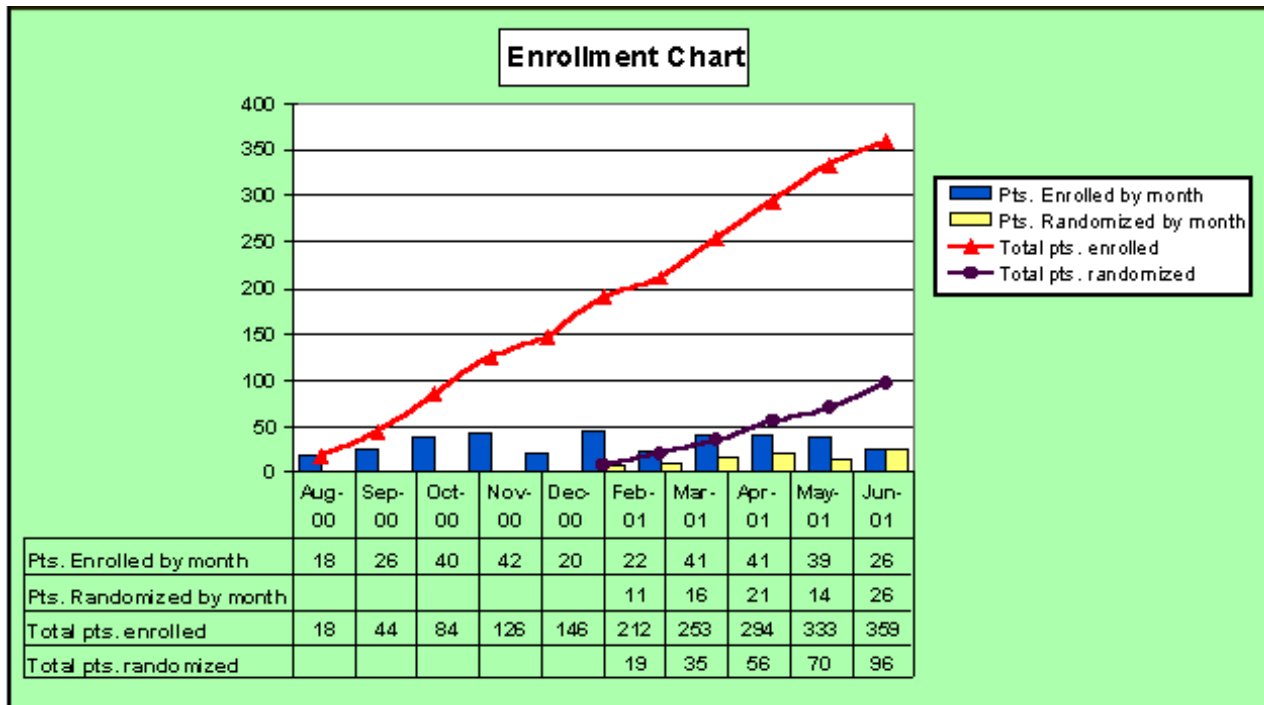
WHY THE HALT-C TRIAL IS A PROSPECTIVE, RANDOMIZED, CONTROLLED TRIAL

By Dr. Herbert Bonkovsky
University of Massachusetts

The main purpose of the HALT-C Trial is to learn whether the potential unpleasant or adverse effects and costs of chronic peginterferon therapy are worth putting up with or not. We don't know whether they are or not. In order to find out, it is important to carry out a trial in which patients with difficult to cure chronic hepatitis C (those still not cured despite treatment with the best currently available treatment) are assigned randomly to receive either no further antiviral treatment (the current standard of care) or to receive chronic, low-dose peginterferon.

It is well known that peginterferon has a number of unpleasant side effects, including muscle aches, fatigue, fever, headaches, insomnia, changes in mood, and many others. It wouldn't make any sense for patients to put up with these for years, nor for them or their insurance companies to pay for the drug for years unless we can prove that there is real benefit to this treatment. As of today, there is absolutely no proof that maintenance interferon therapy provides any long-term benefit for patients with chronic HCV. The only way to determine if this will be effective is to perform this randomized, controlled trial.

Continued on page 4



ISSUES OF INTEREST

Current topics from experts in the field

A PRIMER ON PEGYLATION

By Dr. Herbert Bonkovsky
University of Massachusetts

Throughout the HALT-C Trial, the form of interferon that will be used for treatment will be the pegylated form of interferon alfa-2a developed by Hoffmann-LaRoche (brand name, Pegasys). Just what is pegylation and why use it?

Polyethylene glycol (PEG) is a non-toxic polymer of ethylene glycol that can be excreted readily in the urine. The size of the PEG molecule depends upon the number of repeating ($=\text{CH}_2\text{-CH}_2\text{O}-$) units. These units can be arranged in a strictly linear fashion or there can be branch points in the molecules of PEG, which make them more like a tree with a trunk and side branches. The main purpose of pegylation of proteins is to improve their effectiveness and something called their “therapeutic index.” The therapeutic index is the ratio of the level of a drug at which undesired or adverse (toxic) effects occur divided by the amount needed for the desired therapeutic effect. A higher therapeutic index means that there is a greater margin of safety in the use of a drug.

In general, the hope for pegylation of a drug like interferon is that this will help to maintain therapeutic concentrations for longer periods of time, particularly by reducing the rate of removal of the interferon from the circulation and from other tissues in the body. Pegylation is also hoped to decrease the immunogenicity of interferon (the tendency to lead to an unwanted immune reaction against the drug), and decrease its rate of breakdown within the body.

The main reason why regular short acting interferon was chosen for pegylation is that short acting interferon, even when used daily, is not very effective at curing chronic hepatitis C. Daily or three times a week dosing results in short high peaks of interferon in serum, followed by rapid decreases to zero. Only brief high levels of interferon are achieved with the repeated injection

of interferon alfa-2a (Roferon) three times per week (Figure 1).

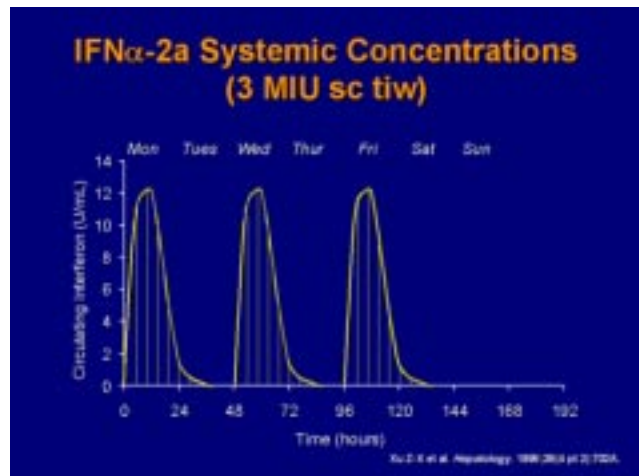


Figure 1.

In contrast, when the interferon is attached to a large branched molecule of polyethylene glycol, the concentrations of interferon in the circulation are prolonged markedly (Figure 2). Figure 2 shows the concentrations of interferon that are achieved after a single initial dose of Pegasys (given at the onset of treatment, the lower curve) and after 48 weeks of treatment, once per week (the upper curve). The reason that the curve after repeated dosing is higher is that it takes time for a long-acting and slowly released drug such as Pegasys to reach a stable concentration. This is actually true of all drugs that are used over extended periods of time. In general, the time needed to reach what is called a “steady-state” concentration of any drug is equal approximately to 4 half-lives of the drug. (A drug “half-life” refers to the time required for the concentration of a drug in the blood to decrease by 50% from its peak value after a single

Continued on next page.

(Primer on Pegylation Continued)

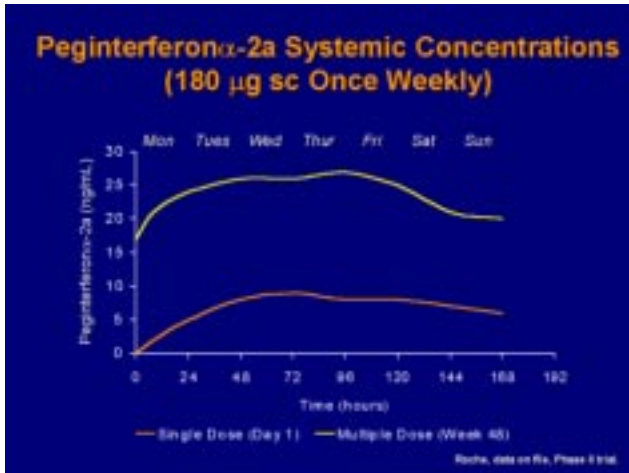


Figure 2.

administration).

A number of studies involving thousands of patients in the U.S. and throughout the world have established clearly that pegylation of interferon, as has been carried out in production of Pegasys, has the desired effect of improving responses of the drug for treatment of hepatitis C, without increasing drug toxicity. In fact, overall, the pegylated interferon is tolerated a bit better than regular interferon given three times per week, with similar but less severe side effects. Because of these desirable pharmacokinetic and clinical effects, the investigators involved in the HALT-C Trial decided that Pegasys was the most effective and best form of pegylated interferon available and therefore, chose it for use throughout the HALT-C Trial.

Did you know...

Inside the liver cells, there are enzymes such as **ALT (SGPT)** and **AST (SGOT)**. When the cells are injured, they break open and the enzymes escape into the blood.

Interferon is a naturally occurring substance your body makes to help defend itself against infection.

The sensitivity of the **qualitative assay** results for HCV is **50 IU/ml**. The sensitivity of the **quantitative assay** results for HCV is **600 IU/ml**.

What Does the Liver Do?

- The liver is a filtering machine, detoxifying and filtering out waste products
- The liver is a refinery, processing foods from the intestine by reshaping proteins into whatever the body needs and making essential chemicals
- The liver is essential for blood clotting
- The liver is a warehouse for storing vitamins, minerals, and iron
- The liver helps digest fats by making bile
- The liver helps maintain hormone balance
- The liver stores sugar for quick energy
- The immune cells in the liver help the body fight infection
- The liver is the main organ of blood formation before birth.



Love Your Liver Tips

- Avoid unnecessary medications.
- Avoid alcohol and illicit drugs.
- When using cleaning products make sure the room is well ventilated and wear gloves.
- Use caution and common sense with intimate contact.
- Get vaccinated against Hepatitis B and A
- Eat a well-balanced nutritionally adequate diet (less deep fried, fatty, salty foods and more high fiber such as fresh vegetables and veggies).
- Regular exercise may help maintain stamina.
- Find out from your study coordinator if there is a support group near you.
- Smile! It may help boost your immune system.

(Taken from the American Liver Foundation at www.liverfoundation.org)



MEET THE STAFF FROM... The University of Massachusetts

Say hello to the staff at the University of Massachusetts Memorial Health Care in Worcester, MA.

Herbert Bonkovsky, M.D.: Principal Investigator
Professor of Medicine, Biochemistry, &
Molecular Pharmacology
Director, The Liver-Biliary-Pancreatic
Center

Raymond Koff, M.D.: Co-Principal Investigator
Professor of Medicine
Director of Clinical Research, The Liver-
Biliary-Pancreatic Center

Savant Mehta, M.D.: Co-Investigator
Assistant Professor of Medicine
Medical Director, Liver Transplantation
Program

Dawn Bombard, R.N.: Research Coordinator

Maureen Cormier, R.N., C.C.R.C.: Research
Coordinator

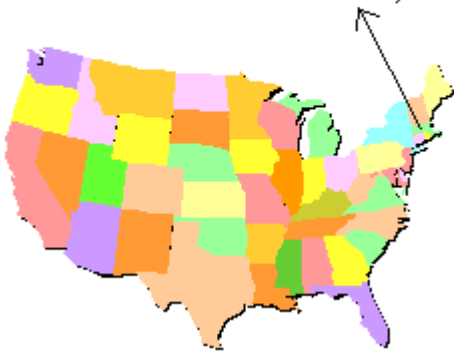
Michelle Kelley, R.N., N.P.: Research Coordinator

Josie Tufo: Lab Services

Barbara Banner, M.D.: Pathologist



Worcester, MA



Coming next Issue:
The staff from The University of Saint
Louis in St. Louis, MO.

(HALT-C Trial Continued)

Enrollment in the HALT-C Trial assures that patients will receive regular, careful follow-up, so that any possible complications of liver disease or of the chronic peginterferon treatment can be managed in the best possible way. It assures that an independent monitoring board of experienced doctors will regularly review what is happening to all patients in the trial in case a worrisome pattern of side effects or problems due to chronic peginterferon develops. Participation in this national trial, sponsored by the U.S. National Institutes of Health, also assures participants that the advice of their coordinators and doctors is free of any possible commercial influence or bias. Finally, it assures that, if any new treatment is established as effective during the course of the trial, all participants (those receiving and those not receiving chronic peginterferon) will receive such new treatment at the earliest possible time. For all these reasons, participants in the HALT-C Trial are assured they will receive the highest possible standard of humane and scientific care.



HALT C NEWS EDITORIAL STAFF

Chair: Recruitment Committee
Mitchell Shiffman, MD
Medical College of Virginia

Data Coordinating Center
Linda Massey

Other Contributors
Herbert Bonkovsky, M.D.
University of Massachusetts
Michelle Kelley, R.N., N.P.
University of Massachusetts

The HALT-C News is a publication of New England
Research Institutes and is published 4 times a year.

Check out the HALT-C Web Site:
WWW.HALTCTRIAL.ORG