

# The Immediate Future Is Pegylated

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# The Immediate Future is Pegylated

By Joe Shaw, HCV Advocate

Remember the '80s tune, "The Future's So Bright (I've Gotta Wear Shades)?"

In sunny San Diego last week, hepatitis C patients might of have been humming this tune.

From a barrage of press releases and studies touting Hoffmann-LaRoche's Pegasys to the optimistic views on new treatments presented by USC's Dr. Karen Lindsay at the Digestive Diseases Week 2000 conference, the future does indeed look reasonably bright for hepatitis C patients.

At a noon press conference on May 22, Lindsay shared with reporters that pegylated interferon was being studied in a number of promising ways in the treatment of Hepatitis C.

"The response we see with peginterferon is at least twice what we see with standard interferon," said Lindsay, Associate Professor of Clinical Medicine at USC's medical school. She led a study that found peginterferon alfa-2b administered once weekly is twice as effective as standard interferon alfa-2b as monotherapy for treating hepatitis C, with similar side effects.

[\(Click here for more information.\)](#)

She also said that preliminary studies show that combined treatment with pegylated interferon and ribavirin were encouraging.

"There's still very little data, very small studies, but from what we've seen, this therapy looks very promising, giving us hope," Lindsay said.

[\(Click here for more information.\)](#)

Another fruitful area for reseach involved stopping the progression of HCV disease in liver tissue. Researchers have known for some time that in patients who respond to interferon, their liver histology improves, leading to lower rates of developing liver disease. Some data has suggested that improvements on liver biopsy may also occur among those without a sustained virologic response.

Lindsay reported on an upcoming study for non-responders. The four-year randomized, controlled study is designed to determine whether continuing Pegasys (peginterferon alfa -2a) for three years will decrease HCV disease progression among non-responders to a second course of anti-HCV therapy. Enrollment will begin this summer at ten clinical centers in the US.

[\(Click here for more information.\)](#)

The May 22 press conference also featured the Mayo Clinic's Dr. W. Ray Kim, who presented a study that found that hospital costs for HCV patients were higher than previously estimated.

Kim found that United States HCV-related hospital costs were \$670 million in 1996. Those costs increase to \$1.3 billion when accounting for other expenses, including physician and out-patient fees. His study also foind that HCV death rates were lower than previous estimates. Kim found that there were approximately 3,200 HCV related deaths per year.

The briefing included a study led by Dr. Thelma Wiley from the University of Illinois found that African Americans infected with chronic hepatitis C have a lower rate of cirrhosis than whites.

Her study's results indicated that over a 40-year period, the African Americans in her study had a significantly slower rate of both fibrosis progression and cirrhosis even though they were infected longer, were older and mostly genotype 1, the hardest HCV genotype to treat.

## **Data Show PEGASYS(TM) (Peginterferon Alfa-2a) May Offer Improved Liver Histology in Hepatitis C Patients**

SAN DIEGO, May 22 -- Data presented this week at Digestive Disease Week (DDW) appear to demonstrate that PEGASYS(TM) (peginterferon alfa-2a), an investigational, longer-lasting form of interferon, may provide significant histologic improvement over standard interferon therapy in chronic hepatitis C patients with cirrhosis. Many researchers believe that patients with histological improvement may have a slower progression of liver disease. Histological response is measured by objective criteria obtained from liver biopsies before and after treatment.

"Patients with cirrhosis are the hardest patients with hepatitis C to treat," said lead investigator Dr. Luis Balart of the Louisiana State University School of Medicine in New Orleans. "Once the liver has the beginning stages of cirrhosis, scar tissue has already formed and, historically, it has been very difficult to improve the histology of the liver cells once that happens."

To date, PEGASYS is the only interferon about which data has been reported to show an increase in the number of cirrhotic patients who achieved a histologic response in a large, controlled study.

The study randomized 271 adult hepatitis C patients with cirrhosis to receive either standard interferon (3MIU three times per week) or PEGASYS (90 mcg. or 180 mcg. one time per week) for 48 weeks with a 24-week follow-up period. Of the 184 patients on whom paired biopsies were performed, 54 percent (37 of 68) of participants who received 180 mcg. of PEGASYS demonstrated a histological response, while only 31 percent (17 of 55) of participants in the standard interferon arm demonstrated a similar response. "Data also suggest that patients who do not achieve a sustained virological response may still benefit from treatment with PEGASYS. Histologic improvements in patients with chronic hepatitis and cirrhosis may lead to slower disease progression," Dr. Balart said.

Recent phase III trial results of PEGASYS presented at the 2000 European Association for the Study of Liver meeting (EASL) showed that 39 percent of chronic hepatitis C patients who received PEGASYS demonstrated a sustained virological response compared to 19 percent who received standard interferon.

### About Pegylation

PEGASYS is made when interferon alfa-2a undergoes the process of pegylation, in which one or more chains of polyethylene glycol (also known as PEG) are attached to another molecule. In PEGASYS, a large, branched, mobile PEG is covalently bound to the interferon alfa-2a molecule and provides a selectively protective barrier without significantly reducing binding site receptivity. Pharmacokinetic behavior depends on the length of the PEG and the structure of the link between the PEG moiety and the protein. Researchers believe the PEG creates a barrier that shields the interferon alfa-2a from being eliminated from the body too rapidly and maintains its ability to consistently suppress the hepatitis C virus over the one-week dosing period. Specifically, clinical trials have demonstrated that PEGASYS may provide longer-lasting levels of drug in the blood -- drug levels following a single dose of PEGASYS last more than one full week (168 hours) as compared to less than 24 hours with standard interferon.

The high molecular weight (40 kilodalton) branched PEG in PEGASYS is believed to provide sustained pegylated interferon alfa-2a exposure at clinically effective levels over the one-week dosing period. In contrast, interferons with smaller PEGs are excreted quickly by the kidneys, requiring more frequent dosing, according to earlier Roche studies, using smaller PEGs developed by the company.

## **Investigational Drug PEGASYS(TM) Selected for Major New National Institutes of Health Study of Chronic Hepatitis C Patients**

NUTLEY, N.J., May 22 /PRNewswire/ -- Hoffmann-La Roche announced today that its investigational drug, PEGASYS (TM) (peginterferon alfa-2a), has been selected by the National Institutes of Health (NIH) for use in a study examining the role of long-term pegylated interferon therapy for the treatment of chronic hepatitis C in patients who failed to respond to previous interferon therapy. Roche recently filed a Biologics License Application (BLA) to the U.S. Food and Drug Administration for approval to market PEGASYS.

The Hepatitis C Antiviral Long-term Treatment to prevent Cirrhosis (HALT-C) Trial will examine approximately 900 patients treated with interferon over three-and-a-half years. The study is designed to determine if long-term interferon therapy with PEGASYS can reduce the risk of histologic progression to cirrhosis, decompensated liver disease and/or hepatocellular carcinoma in patients with chronic hepatitis C and advanced fibrosis or cirrhosis who failed to respond to previous interferon therapy.

Currently available treatment for hepatitis C includes monotherapy with interferon alpha and combination therapy of interferon with ribavirin. Patients with hepatitis C who do not experience a response while taking either monotherapy or combination therapy generally do not remain on the treatment.

"Right now, patients who discontinue interferon therapy are left without options. As a result, they are at risk for developing liver diseases associated with hepatitis C, including decompensated cirrhosis and liver cancer," said Chris Pappas, MD, medical director, Hoffmann-La Roche. "Some of these patients become so ill that they require liver transplants."

"Because this study will evaluate whether there are benefits to continuing treatment with interferon among the patients considered 'non-responders,' researchers at NIH may uncover valuable new information about the management of hepatitis C," continued Dr. Pappas.

Screening for the HALT-C Trial will begin in June. Trial centers will be located in California, Colorado, Maryland, Massachusetts, Michigan, Missouri, Texas and Virginia.

### **Current Data on PEGASYS**

To date, Roche has conducted several clinical trials with PEGASYS. In three pivotal clinical studies involving a total of more than 1,400 patients, those treated with 180 mcg of PEGASYS had overall sustained virological responses of 35 percent in patients without cirrhosis and 30 percent in patients with cirrhosis. Virological response was defined as undetectable HCV RNA as measured by the AMPLICOR HCV Monitor(TM), version 2.0.

In the largest prospective study (n=271) to include only hepatitis C patients with cirrhosis -- the most difficult group of hepatitis C patients to treat -- data showed that PEGASYS may achieve a sustained response rate nearly four times higher than standard interferon -- 30 percent (26 of 87) versus 8 percent (7 of 88).

In addition, data from two other studies show that patients treated with PEGASYS obtained improved liver histology in post-treatment liver biopsies. In a study examining 184 adult hepatitis C patients with cirrhosis, 54 percent (37 of 68) of patients who received 180 mcg of PEGASYS demonstrated a histological response, while only 31 percent (17 of 55) of participants in the standard interferon arm demonstrated a similar response. In a study examining histology in 114 non-cirrhotics, 63 percent (19 of 30) of patients who received 180 mcg of PEGASYS demonstrated a histological response, versus 57 percent (13 of 23) who received standard interferon. Many researchers believe improved histology may be associated with slowing the progression of liver disease.

In addition to the virologic and histologic PEGASYS trials, a self-rated health improvement survey evaluating the quality of life (QoL) of patients with chronic hepatitis C showed improved scores among those treated with once- weekly doses of

PEGASYS versus those treated with thrice-weekly doses of standard interferon alfa-2a.

Results were collected in a randomized, controlled clinical trial (n=250) comparing PEGASYS to standard interferon. When asked to rate their general health compared to one year before, 48 percent of patients treated with PEGASYS reported feeling "better" or "much better," compared to 26 percent for standard interferon. The data were collected using a standardized 36-question short form (SF-36) health survey. Among those demonstrating a sustained viral response to PEGASYS, scores on the physical component of the survey - including measures of vitality, physical functioning, bodily pain, general health and social functioning - improved by two points, from 46.1 to 48.9. Scores in this study were recorded at pretreatment and at end of treatment (at week 48).

Adverse events with PEGASYS are similar to those seen with standard interferon regimens, such as fatigue, headache, myalgia/arthralgia, flu-like symptoms, nausea/vomiting, fever, chills, diarrhea, partial alopecia, abdominal pain, depression, irritability, insomnia, and anorexia.

## THE NATURAL HISTORY OF HEPATITIS C IN AFRICAN AMERICANS

Thelma E. Wiley, Jennifer L. Brown, Antonios Sapounas, Ravi Moparty, Juliana Chan, Univ of Illinois, Chicago, IL.

Background Hepatitis C (HCV) infects 1-3% of the United States population. African Americans(AA)are disproportionately infected with this virus (5%) and predominately infected with genotype 1 HCV. The natural history of this disease in AA has not been analyzed in a large number of HCV infected patients. Aim To analyze demographic, virological, biochemical and histological data in order to determine the natural history of liver disease in AA versus non-African Americans (non-AA). Methods We retrospectively reviewed the records of 289 patients with HCV seen at our institution from 1996 through 1999. We included patients who had adequate histological data to assess HAI and the degree of hepatic fibrosis. The following data were collected: age, gender, race, weight, baseline ALT, genotype, HCV RNA levels, mode and duration of infection. The duration of infection was estimated from earliest potential exposure to the virus. Liver biopsies were reviewed (blindly) and graded for histologic activity using the Knodell scoring system (HAI). Results There were 93 AA and 196 non-AA patients. There were no significant differences in mean baseline HCV RNA and weight. Although not significant, only 23% of AA's compared to 31% of non-AA's were cirrhotic. There was a significant difference between AA and non-AA patients in piecemeal necrosis (PN)(2.5 vs. 3.1,  $p=.04$ ), mean baseline ALT(86.55 vs. 112.41,  $p=.01$ ), age (49 vs. 45,  $p=.001$ ), and duration of infection(27 vs. 23,  $p=.002$ ). AA patients were more often infected with genotype 1 HCV (87.7% vs. 70.9%,  $p=.02$ ) No AA patients were infected with genotype 3 HCV. When analyzing the data according to the duration of infection, AA patients had a lower ALT(56 vs. 134,  $p=.03$ ), total HAI(3.1 vs. 4.8,  $p=.05$ ), as well as portal inflammation (1.4 vs. 2.4, $p=.02$ ), PN(.8 vs. 3.1,  $p=.05$ ), and HAI without fibrosis(3.5 vs. 6.6,  $p=.04$ ) during the second decade of exposure (years 10-19). There were no AA patients with cirrhosis by the second decade compared to 26% of non-AA patients with cirrhosis, although this was not statistically significant. By the third decade (years 20-29), 18% of AA patients vs. 31% of non-AA's were cirrhotic. The degree of fibrosis was significantly greater in non-AA patients (2.1 vs. 2.6,  $p=.04$ ). Summary AA's are more likely to be infected with genotype 1 HCV and tend to progress more slowly to cirrhosis. In addition, early in their exposure, AA's had lower HAI, baseline ALT, and percentage of cirrhosis, although mean baseline HCV RNA levels and weight were not significantly different.

# Study Finds Pegylated Interferon Alfa-2b Twice as Effective as Standard Interferon Monotherapy

SOURCE: University of Southern California Press Release

SAN DIEGO, May 22 -- The results of a worldwide multi-center clinical trial indicates that patients with hepatitis C, a virus that causes potentially fatal liver disease, may soon have access to a new treatment option. The study results were presented yesterday at the Digestive Disease Week meeting in San Diego.

The study, led by Karen L. Lindsay, MD, Associate Professor of Clinical Medicine, Gastrointestinal and Liver Diseases at the Keck School of Medicine of the University of Southern California, found that peginterferon alfa-2b administered once weekly is twice as effective than standard interferon alfa-2b as monotherapy for treating hepatitis C, and was just as well tolerated. The current "gold standard" of treatment for hepatitis C is combination therapy with interferon alfa-2b, administered three times weekly with daily doses of oral ribavirin.

"The results of this study are very promising for hepatitis C patients," said Dr. Lindsay. "Since peginterferon alfa-2b has been shown to be effective alone, we anticipate that it may be even more effective when used in combination with ribavirin. I expect this combination therapy to become the optimal treatment for hepatitis C in the future." Combination therapy with peginterferon alfa-2b and ribavirin is currently in Phase III clinical trials.

Pegylation involves the attachment of polyethylene glycol to the interferon molecule. Pegylation results in slower clearance of the interferon molecule, allowing it to remain in the bloodstream longer, therefore providing a more convenient once-weekly dosing schedule for patients.

Hepatitis C, when left untreated, can lead to cirrhosis (scarring of the liver), liver failure and death, as well as primary liver cancer. It is the leading cause of liver transplantation in the United States and patients often remain without specific symptoms for as long as three decades. Hepatitis C is the most common blood borne infection in the United States, and is estimated to infect nearly 4 million Americans. Approximately 10,000 Americans die from chronic liver disease due to hepatitis C annually, and that death rate is expected to triple in the next 10 to 20 years.

## Study Details

The aim of the multi-center clinical trial was to establish the safety and effectiveness of peginterferon alfa-2b in comparison to standard interferon alfa-2b. Participants had never been treated for hepatitis C prior to this study.

Patients participating in the study were divided into four groups, receiving either 0.5 ug/kg, 1.0 ug/kg, or 1.5 ug/kg of peginterferon alfa-2b once weekly, or the standard dose of interferon alfa-2b (three million international units three times weekly).

Results showed that patients treated with all doses of peginterferon alfa-2b had significantly lower levels of detectable virus during treatment, at the end of treatment, and after 24 weeks of follow up, than the group who received the standard interferon. Patients in the peginterferon alfa-2b groups achieved sustained virologic responses (no detectable virus in the blood for 24 weeks after discontinuing treatment) of 18%, 25% and 23% respectively, compared to 12% for the standard interferon group. However, combination therapy with standard interferon alfa-2b and ribavirin remains the most effective treatment available, with sustained virologic response rates of about 40%.

"Once approved for marketing, peginterferon alfa-2b will be another important addition to the hepatitis C treatment arsenal," said Dr. John McHutchison, Medical Director of Liver Transplantation at the Scripps Clinic and Research Foundation in La Jolla, CA and a participating investigator in the study. "The once weekly dosing schedule should make treatment more convenient for patients with hepatitis C, and improve patient compliance."

SOURCE: University of Southern California