

## **HALT-C Trial Shows Minimal Long-term Benefit of Pegylated Interferon Alfa-2a (Pegasys) Maintenance Therapy in Patients with Chronic Hepatitis C**

Combination therapy with pegylated interferon plus ribavirin produces sustained hepatitis C virus (HCV) suppression in about half of all patients (less for HCV genotype 1, more for genotypes 2 or 3).

Over time, chronic HCV infection can progress to advanced liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC), end-stage liver disease, and death due to liver failure. Since interferon-based therapy does not always eradicate the virus, researchers have explored various strategies for reducing or reversing liver disease progression even in the absence of sustained virological response (SVR).

The large HALT-C (Hepatitis C Antiviral Long-term Treatment against Cirrhosis) study aimed to determine whether extended maintenance with pegylated interferon monotherapy could prevent progressive liver disease among hepatitis C patients who did not respond to combination therapy. Results were presented in a late-breaker session at the recent 58th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in Boston.

Researchers from multiple U.S. centers conducted a randomized controlled trial in which 1050 patients with chronic hepatitis C and advanced fibrosis who were non-responders to prior therapy with pegylated interferon plus ribavirin were randomly assigned to received either 90 mcg once-weekly pegylated interferon alfa-2a (Pegasys) for 3.5 years or no further treatment. For comparison, the usual Pegasys dose in combination therapy is 180 mcg once-weekly for 24 (genotypes 2/3) or 48 (genotype 1) weeks.

Participants eligible for enrollment had an Ishak fibrosis score of > 3 on liver biopsy, a Child-Turcotte-Pugh score of >6, no history of ascites, encephalopathy, or bleeding varices, and no other identifiable cause of liver disease. Participants were stratified according to their stage of fibrosis: Ishak stage 3 or 4 (622 with fibrosis) vs 5 or 6 (428 with cirrhosis).

Participants were seen at 3-month intervals, underwent liver biopsies at 1.5 and 3.5 years after randomization, and were monitored for the occurrence of death, HCC, hepatic decompensation (variceal hemorrhage, ascites, spontaneous bacterial peritonitis, encephalopathy, or a Child-Turcotte-Pugh score of = 7), and -- for those with pre-cirrhotic fibrosis at baseline -- an increase in fibrosis score of = 2 points.

### **Results**

- By the end of the study, 34.1% of patients in the pegylated interferon maintenance arm and 33.8% of the control group had reached one of the study endpoints (hazard ratio 1.01; P = 0.91; not a significant difference).
- Although mean serum ALT and HCV RNA levels decreased significantly with treatment (both P < 0.0001), as did necroinflammatory changes on liver biopsy (P < 0.0001), there was no significant difference observed in rates of any of the primary outcomes:
- Death: 6.6% in the treatment group vs 4.6% in the control group;

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Results (continued from previous page)

- Hepatic decompensation: 14.3% vs 13.2%, respectively;
- HCC: 2.8% vs 3.2%;
- Increased fibrosis: 28.2% vs 31.9%.
- The rate of serious adverse events was similar in both groups: 284 events among 175 treated patients and 283 events among 155 control subjects.
- Among treated patients, 17% stopped pegylated interferon maintenance by 1.5 years and 30% discontinued by 3.5 years.

### **Conclusion**

“Long-term therapy with peginterferon did not reduce the rate of disease progression,” the investigator concluded. “These findings do not support maintenance therapy with peginterferon in patients with chronic hepatitis C and advanced hepatic fibrosis who are non-responders to a course of peginterferon/ribavirin therapy.”

Previously presented interim results from HALT-C looked promising, since pegylated interferon maintenance therapy led to improvements in ALT level, HCV viral load, and necroinflammation -- surrogate markers that are often assumed to predict liver disease progression. However, while these results held, they ultimately did not translate into a lower likelihood of fibrosis progression, liver cancer, liver failure, or death.

This is supported by data from a similar study of pegylated interferon alfa-2b (PegIntron) maintenance monotherapy presented at the same conference, which showed improvements in necroinflammation and fibrosis scores, but no reduction the rate of serious liver complications including decompensation and HCC.

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AM Di Bisceglie, ML Shiffman, GT Everson, and others. Prolonged Antiviral Therapy With Peginterferon to Prevent Complications of Advanced Liver Disease Associated With Hepatitis C: Results of the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial. 58th Annual Meeting of the American Association for the Study of Liver Diseases. Boston. November 2-6, 2007. Abstract (oral) LB1.