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Hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial

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Abstract

Background: **In patients with chronic hepatitis C who do not have a response to antiviral treatment, the disease may progress to cirrhosis, liver failure, hepatocellular carcinoma, and death. Whether long-term antiviral therapy can prevent progressive liver disease in such patients remains uncertain.** ***Methods:*** **We conducted a randomized, controlled trial of peginterferon alfa-2a at a dosage of 90 μg per week for 3.5 years, as compared with no treatment, in 1,050 patients with chronic hepatitis C and advanced fibrosis who had not had a response to previous therapy with peginterferon and ribavirin. The patients, who were stratified according to stage of fibrosis (622 with noncirrhotic fibrosis and 428 with cirrhosis), were seen at 3-month intervals and underwent liver biopsy at 1.5 and 3.5 years after randomization. The primary end point was progression of liver disease, as indicated by death, hepatocellular carcinoma, hepatic decompensation, or, for those with bridging fibrosis at baseline, an increase in the Ishak fibrosis score of 2 or more points.** ***Results:*** **We randomly assigned the patients to receive peginterferon (517 patients) or no therapy (533 patients) for 3.5 years. The level of serum aminotransferases, the level of serum hepatitis C virus RNA, and histologic necroinflammatory scores all decreased significantly (P < 0.001) with treatment, but there was no significant difference between the groups in the rate of any primary outcome (34.1% in the treatment group and 33.8% in the control group; hazard ratio, 1.01; 95% confidence interval, 0.81 to 1.27; P = 0.90). The percentage of patients with at least one serious adverse event was 38.6% in the treatment group and 31.8% in the control group (P = 0.07).** ***Conclusions:*** **Long-term therapy with peginterferon did not reduce the rate of disease progression in patients with chronic hepatitis C and advanced fibrosis, with or without cirrhosis, who had not had a response to initial treatment with peginterferon and ribavirin.**

Key words: Hepatitis C, peginterferon, maintenance therapy, cirrhosis.

Article commented:

Di Bisceglie AM, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, Lee WM, Lok AS, Bonkovsky HL, Morgan TR, Ghany MG, Morishima C, Snow KK, Dienstag JL; HALT-C Trial Investigators. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med. 2008;359:2429-41.

Introduction

Chronic hepatitis C virus (HCV) infection is a worldwide major health problem. It is a major cause of cirrhosis , hepatocellular carcinoma (HCC) and the most common indication, by far, for liver transplantation in Canada and the United States. Despite the fact that anti-viral therapy has evolved over the years, with the current commercially available drugs, ie. peginteferon (pegIFN) and ribavirin, the sad fact remains that at least half of the patients do not achieve a sustained virologic response (SVR) will be at risk for eventual progression to cirrhosis and HCC. This treatment is also associated with considerable adverse effects and is very costly (in Canada, 48 weeks of pegIFN and ribavirin has an associated cost of approximately $15,000 Cdn). Given that half of all patients will not achieve a SVR with the currently licensed drugs, the question that both patients and clinicians alike ask is if anything can be done for those who are pegIFN and ribavirin treatment failures and can the pro-

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gression to end-stage liver disease be averted? It was therefore with this question in mind that we comment on the recently published HALT-C study.[1]

The HALT-C was a large, prospective, randomized, controlled trial of long-term low dose peg interferon therapy in patients with advanced hepatitis C who had not had a sustained virologic response to a previous course of interferon-based therapy. To ensure that all patients randomized to maintenance pegIFN alfa 2a at a dose of 90 μg weekly, *vs* no treatment, were true failures to pegIFN and ribavirin, all patients were given a 24 week course of standard therapy before randomization and only those who were HCV RNA detectable were randomized at week 20. The trial was designed to assess whether maintenance pegIFN could at least prevent progression to cirrhosis/progression of fibrosis and clinical progression of decompensated disease/HCC as a primary study outcome. Despite long duration of treatment primary outcome occurred in 34.1% of the treatment group and 33.8% of the control group and importantly, pegIFN therapy did not reduce the incidence of hepatocellular carcinoma in patients with advanced fibrosis and persistent viremia even when maintained for several years.[1] Although there was a statistically significant biochemical improvement in the treatment arm *vs* the observational arm, essentially, there was absolutely no benefit with regards to the clinically important end-points.

Although the overall outcome of the HALT-C study is very disappointing, important points can be drawn. First of all, it is clear that there is no role for maintenance pegIFN therapy in those who are non-responders to pegIFN and ribavirin. These patients, can therefore be spared the side effects, as well as the risk of acute treatment-associated decompensation, the poor quality of life while on therapy and the expense of treatment that the HALT-C investigators have no definitively demonstrated to be futile. The study also finally puts to rest the question, raised by prominently cited retrospective studies,[2,3] that even if patients do not achieve a SVR, the risk of HCC is reduced. In the HALT-C study, approximately equal numbers developed HCC in both arms. Interestingly, a small number of non-cirrhotic patients (ie. 2.1%) developed HCC suggesting that all patients with advanced fibrosis should be considered for regular abdominal ultrasound HCC surveillance.

Lastly, is there anything that can be done for pegIFN treatment failures? This question depends on the definition of treatment failure. For relapsers to pegIFN and ribavirin (ie. those who were HCV RNA negative at the end of therapy but relapsed six months post-therapy), new studies suggest that these patient may have a reasonable chance of achieving a SVR with a second course of pegIFN and ribavirin.[4,5] These same studies demonstrate that for true non-responders (ie. those who were HCV RNA positive at the end of therapy), the likelihood of achieving a SVR with a second course of therapy is very small (ie. 7-14%). These patients will clearly need to wait for the new anti-viral treatments on the horizon of on-going clinical trial. For these patients who can afford to wait, the future indeed looks bright as clinical trials have just begun on some promising HCV-targeted compounds, such as the substrate specific NS3-4A protease inhibitors (telepravir) or the NS5B polymerase inhibitors (boceprevir) in combination with pegIFN and ribavirin. A first interim analysis on SVR after treatment with telaprevir in combination with pegylated interferon-alfa and ribavirin has recently been presented, and the results are promising. It has shown that combination therapy with telaprevir with pegylated interferon-alfa plus ribavirin may not only increase the rate of SVR compared with standard therapy but may also allow a decrease of treatment duration.[6] A new treatment-paradigm with Boceprevir has shown the potential to maximize efficacy of multi-drug combinations and minimize the risk of resistance by identifying responders to PEG/RBV. Four weeks of treatment with PEG/RBV prior to boceprevir administration markedly increased RVR (Rapid virologic response – HCV RNA negative at week 4) and EVR(Early virologic response – HCV RNA negative at week 12) and reduced viral breakthrough by 50%.[7]

For those non-responders with established cirrhosis, it will be a few years before these novel new anti-viral agents appear on the market, In the interim, the best strategy for these patients should be watchful waiting: monitoring for signs of decompensation with a view to possible referral to a liver transplant centre and regular ultrasound monitoring for HCC.

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